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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

SIXTEENTH SESSION,

HELD AT WASHINGTON, D. C.,

APRIL 30, AND MAY 1 AND 2, 1901.

VOLUME XVI.

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I. E. Atkinson,
A. B. Ball,
L. F. Barker,
G. Baumgarten,
H. M. Biggs,
F. Billings,
A. D. Blackader,
C. S. Bond,
J. W. Brannan,
R. C. Cabot,
Charles Cary,
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F. Delafield,
George Dock,
H. C. Ernst,
J. Ewing,
S. Flexner,
F. Forchheimer,
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F. P. Henry,
C. A. Herter,
L. E. Holt,
Henry Hun,
H. M. Hurd,
A. Jacobi,
W. B. James,
E. G. Janeway,
W. W. Johnston,
F. P. Kinnicutt,
H. Koplik,
T. S. Latimer,
M. J. Lewis,
S. Loving,
A. McPhedran,
S. J. Meltzer,
J. K. Mitchell,
J. H. Musser,
W. P. Northrup,
F. G. Novy,
Wm. Osler,
F. A. Packard,
W. H. Park,
G. L. Peabody.
F. Pfaff,
T. M. Prudden,
J. J. Putnam,
W. Reed,
B. Robinson,
B. Sachs,
F. C. Shattuck,
M. A. Starr,
A. Stengel,
G. M. Sternberg,
D. D. Stewart,
J. Stewart,
C. G. Stockton,
J. S. Thacher,
W. S. Thayer,
E. L. Trudeau,
J. Tyson,
V. C. Vaughan,
H. P. Walcott,
W. H. Welch,
F. H. Williams,
J. C. Wilson,
J. H. Wright,

TUESDAY, APRIL 30TH—MORNING SESSION.

The Association was called to order at 11 A.M. by President Welch, who delivered the following INTRODUCTORY ADDRESS:

Even if there were any temptation to deviate from the salutary custom of most of my predecessors in this office and to inflict upon you an address of a general character on this occasion, a glance at our full programme would make clear the cruelty of such a proceeding. The insertion from year to year at the beginning of our programme of an "Address by the President" must be intended mainly for decorative effect.

We are here to listen to papers which bring actual contributions to medical knowledge and to discuss them.

It is true that when it is recalled that this is the first meeting of our Association in the new century, and that it is just fifteen years since we first met, one is tempted to cast a look before and after; but any attempt at such a retrospect and outlook would lead so far that it does not seem worth while to take up this theme, and perhaps most of the thoughts suggested by it are obvious enough.

Before I fully realized the importance of encroaching as little as possible upon the time devoted to the scientific work of the Association, I had in mind certain subjects which seemed appropriate for an address, and to one of these lines of thought it may not be out of place to refer in these opening remarks, although it must be without elaboration.

It would, I think, be of interest to compare the opportunities at present afforded in this country for the training and careers of those who intend to take up as their life-work one of the medical sciences, such as anatomy, physiology, and pathology, with the opportunities open to those who desire to fit themselves for the higher positions in clinical medicine or surgery.

We now have in this country far from enough, but still a fair number, of well-equipped and properly organized laboratories representative of each of the fundamental medical sciences, and I venture to say that in these the thoroughness of laboratory training for students compares favorably with that provided anywhere in the world. In astonishingly few years the laboratory side of our teaching has advanced in several of our institutions from the weakest to the strongest feature of the medical curriculum.

But what I wish now to emphasize is not the undergraduate instruction, but rather the facts that a young man who chooses for his career one of

the scientific subjects can find in several places in this country the opportunities and training to make him a good anatomist, physiologist, or pathologist, and if he succeeds in winning his spurs he can look forward with reasonable assurance to securing a desirable position as a teacher and a director of a laboratory of his special branch of science. He must serve his apprenticeship as an assistant for five, ten or more years, the conditions being much like those for promotion in the German universities.

All of this is a gratifying advance over former conditions. It is true that we are only at the beginning of this direction of development, but the path has been opened and entered upon, and the lines of advance are clearly marked out.

Now, how is it with similar opportunities for the far larger number of young physicians who wish to fit themselves for corresponding careers in clinical medicine and surgery? In general the only path open to them is through family practice and work in a dispensary, supplemented, perhaps, by some laboratory work. While this may lead to the desired end, it does not seem to me the method adapted to secure the best results. In two respects there is a striking contrast between these conditions and those which prevail in the making of anatomists, physiologists, and pathologists, viz.: in the opportunities and methods for thorough and prolonged scientific training and in the chances of promotion.

With one or two exceptions our hospitals do not offer the requisite opportunities to young men who aim at the higher careers in clinical medicine and surgery. Over the ordinary internes there should be salaried resident positions of greater permanence and responsibility to enable promising young men to do scientific work, to acquire thorough clinical experience, and to begin to establish their reputations by contributions to their special departments of knowledge. During this period, which should be one of productive work, their positions would be analogous to those of assistants in laboratories, and, as in the latter case, should bring to the front those of demonstrated ability. The reorganization of the medical staff of the hospital necessitated by the change suggested should, moreover, increase its practical and scientific efficiency.

Furthermore, with the present organization of our medical schools and hospitals there is but little chance that a clinician who has acquired a high reputation in one place by his scientific work in medicine or surgery will be called to a vacant position elsewhere; whereas, our medical schools now look the country over to find the best man available to fill a vacancy in the chairs of anatomy, physiology, or pathology.

It would seem, then, that the training of physicians and surgeons has not kept pace with the progress of medical science to the same degree as has that of specialists in the more purely scientific branches. I should like to discuss this subject more fully, as I am fully aware of the controversial points raised; but before such a body of physicians and pathologists as this it may suffice to have drawn attention to a matter which, although not new, seems to me of an importance not fully and generally recognized.

There is one point more personal to the immediate interests of this Association to which I must refer, although it has been repeatedly touched upon by my predecessors. This is the pressure upon our doors for admission by a large number of active workers in clinical medicine, pathology, and bacteriology, many of whom would make desirable members. It does not seem to me expedient to extend further, at least for the present, the limit of membership.

As was said by Dr. Delafield, our first President, in his opening remarks: "We want an association composed of members, each one of whom is able to contribute something real to the common stock of knowledge, and where he who reads such a contribution feels sure of a discriminating audience." It is important for the maintenance of these standards that those members who are unable to attend the meetings with some degree of regularity, or to make occasional contributions, either of papers or to the discussions, should realize the congestion of our ranks and the consequent exclusion of desirable men seeking admission. If all to be recommended by the Council should be elected at this meeting the limit of membership will be reached.

In this connection I should like to echo a suggestion made by a former President, the lamented Dr. Da Costa, who in discussing this matter said: "The question I ask to present to you is, Whether we could not make a freer use of our honorary list and transfer to it those who have been members for a long time, but find it inconvenient to attend with regularity, yet wish to remain with us? By so doing there would be a larger number of vacancies on our active list." This suggestion seems to me well worthy of consideration.

We have rarely met without our flag at half-mast on account of the death of some of our members, but never before have we had to mourn losses so great as those which we have sustained since our last meeting. During this period there have passed away one of our honorary members and four of the founders of this Association, including three of its former Presidents—Stillé, Whittaker, Da Costa, Busey, and Draper.

These were honored leaders in our profession, influential teachers, distinguished practitioners and consultants, active contributors to medical knowledge, and faithful and zealous friends of this Association. It is not a little remarkable that all belonged to the group of humanists who have adorned so much our profession by their scholarly attainments, and whose active interests extend beyond the domain of medicine to literature, science, and art. The record of their lives and achievements is so well known to the medical world, and especially so familiar to all of us, that I need not enter into biographic details, and the words of tribute and characterization must through lack of time necessarily be few.

Alfred Stillé (1813–1900), who was one of our seven original honorary members, belonged to that interesting group of American pupils of Louis who, bringing back the scientific spirit and the methods of their master, introduced the new medicine in Boston, New York, Philadelphia, and Baltimore during the fourth decade of the past century. But he did not go empty-handed to Paris, for this young physician, fresh from service in Gerhard's wards in the Philadelphia Hospital, made known in France, in a paper read before the Société Médicale d'Observation in 1838, the important observations of Gerhard which established the distinction between typhoid fever and typhus fever. Stillé was a teacher of medicine for forty years, holding for twenty years the Professorship of the Theory and Practice of Medicine in the University of Pennsylvania. His views on medical education were enlightened and, indeed, in some respects, in advance of the time of their publication. He was a close and accurate clinical observer, a thoughtful and laborious student, a physician of high ideals, deservedly honored by his colleagues throughout his long and useful life. Of his many publications there may be mentioned as of special importance his standard treatise on *Therapeutics and Materia Medica*, which passed through four editions and was translated into German; *The National Dispensatory*, by Stillé and Maisch, a work of great service to physicians as well as to pharmacists; and his valuable monograph on *Epidemic Meningitis*, which serves as a good example of his scholarly method, clear and finished style, and precise observation. As physician, writer, and teacher, Alfred Stillé has a secure position in the annals of American medicine.

James T. Whittaker was stricken with a fatal disease in the fulness of his powers, and the wish expressed in his Christmas story, "Exiled for Lèse Majesté," "Anyone would prefer to go before his opinions are as petrified as his arteries," was amply fulfilled for him. He was endowed with unusual energy, enthusiasm, optimism, and an unswerving

devotion to his life-work. He was always among the first to seize and apply important new ideas in medicine, as was well illustrated by his hastening to Berlin to study with Koch immediately after the announcement of the discovery of the tubercle bacillus, and by the prompt and interesting reports which he made upon this subject, as well as by his later studies on the use of tuberculin. From the date of the publication of his prize essay in 1870 on *The Morbid Anatomy of the Placenta* up to his final illness he published many and valuable contributions. We shall miss sadly his participation in our meetings.

What need I say before this Association of Jacob M. Da Costa? We were proud of him as the brightest ornament of the medical profession of this country, whose fame was world-wide and will endure throughout the annals of American medicine. He will be remembered not only as a teacher, an author, a diagnostician, and consultant of great excellence, but also as a man of rare gifts of character, of culture, and of personal charm. His originality and powers of accurate observation and keen analysis were early exhibited in his studies of cancer of the pancreas, and still more strikingly a little later by his studies on the heart of soldiers in the civil war, which led to his epochal work *On Strain and Over-action of the Heart.* Of his publications, all of value, he is best known by his text-book on *Medical Diagnosis*, which has passed through nine editions and been translated into several foreign languages, having achieved the greatest success of any American text-book. I need not recall with what delight and instruction we listened to Dr. Da Costa in these meetings, the last of which he attended a year ago. His unexpected death came as a shock to all. He has left a record of high achievement and an example of the best type of physician and man.

It is peculiarly fitting that words of appreciation of Samuel C. Busey should be uttered in this city, where his long professional life was spent, and where he will be long remembered both as a physician and a public-spirited citizen. He was a man of dominant personality, of lofty ideas, of broad views, of untiring industry, and of unusual organizing ability. He did not begin to publish until his forty-first year, when he had acquired a ripe experience. There followed 163 distinct contributions to medical literature, the most numerous and important relating to obstetrics and diseases of women and children. Especially noteworthy are his papers and monographs on diseases of the lymph-channels and on the unjustifiability of craniotomy upon the living fetus. The history of medical legislation and of sanitation in the District of Columbia is inseparably connected with the name of Dr.

Busey. What he says in his charming autobiographic souvenir is true: "I have uniformly contended for the honor and dignity of the medical profession, which I have believed could be more effectively maintained by the dicta of a high *esprit de corps* than by the penal provisions of a code of ethics but rarely enforced; that the highest standard of medical education was demanded by every consideration of professional duty and obligation, and that the profession should assert its prerogatives of right and power, in that legislators and all others in authority should come to know that science must dominate public opinion in all matters pertaining to preventive and remedial medicine." During the last six years of his life Dr. Busey was physically disabled as the result of an unfortunate accident, and he then found solace in literary pursuits which led to the publication of historic and biographic works of much interest and value. Not only this community but the whole nation owe to Dr. Busey a debt of gratitude for his public services to the national capital.

Only yesterday was borne to his last resting-place one of the most universally esteemed and loved of our members—William H. Draper. Of singularly attractive personality, graceful and dignified in speech and bearing, scholarly in attainments, he was one whom his colleagues always delighted to have as their representative on important public occasions, and upon whom our choice naturally fell to preside over this Association at that first notable Congress of American Physicians and Surgeons. In hospital and in private practice he was the successful and beloved physician, whose loss is now deeply mourned by many to whom he had ministered in sickness. His more immediate interests were in clinical medicine, to which he made valuable contributions, especially on the subjects of thermometry, gout, disorders of nutrition, and dietetics; but he was generously appreciative of all good work in medicine, and as President of the Alumni Association of the College of Physicians and Surgeons and as trustee of Columbia University he did much to foster the development of laboratories and of scientific work in that institution. He was deeply interested in the welfare of this Association, by whose members he will always be held in affectionate remembrance.

In turning now to the scientific work of the Association, permit me to call attention to the large number of papers upon our programme. It will be possible to complete the reading of all the papers only by brevity on the part of the readers and the participants in the discussions. I shall feel called upon to enforce strictly the time limits pre-

scribed by our by-laws, and I must ask that extension of time be not requested. May I make the suggestion that a paper in the shape most suitable for publication is not always in the form best adapted for presentation to an audience, and especially that historic matter, detailed clinical records, and protocols of experiments can often be omitted, or at least very much abbreviated, to the advantage both of the reader and of the hearers. There is abundant promise in the subjects on our programme and in the names of those who are to present them that we shall be rewarded by an instructive and successful meeting.

The Secretary read the list of nominees recommended by the Council for election to membership.

The Treasurer read his annual report, which was referred to an auditing committee consisting of Drs. Abbott and Cabot.

Dr. Hare read a paper entitled "An Undescribed Cardiac Sound," which was discussed by Dr. Osler.

Dr. Thayer read a paper entitled "The Frequency and the Diagnosis of the Flint Murmur in Aortic Insufficiency," which was discussed by Drs. Cabot and Tyson.

Dr. Stengel read a paper entitled "The Unilateral, and Especially the Right-sided, Occurrence of Hydrothorax in Cardiac Disease," which was discussed by Drs. Osler, Wilson, Janeway, Hare, Jacobi, and Stengel.

Dr. Robinson read a paper entitled "Myocarditis and Fatty Degeneration of the Heart."

Dr. Jacobi read a paper entitled "Hemorrhage from a Pleural Abscess," and one entitled "Cyst of the Omentum," which were discussed by Drs. Kinnicutt, Henry, Peabody, Shattuck, Osler, and Jacobi.

Dr. Cary read a paper entitled "A Case of Lobar Pneumonia Complicated by Pseudomembranous Exudate on the Mucous Membranes of the Mouth, Tongue, Pharynx, Nares, Conjunctivæ, Glans Penis, Anus, etc., Caused by Diplococcus Pneumoniæ."

Adjourned at 1.25 P.M.

Afternoon Session.

The Association was called to order at 2.40 P.M. by President Welch.

The Auditing Committee reported that they had examined the Treasurer's accounts and vouchers and had found them correct.

Dr. Henry read a paper entitled "Further Notes of a Case of Pernicious Anemia Reported at the Meeting of 1900."

Dr. Billings read a paper entitled "Report of the Progress of Cases of Pernicious Anemia presented to the Association in 1900, and Report of a Case of Pernicious Anemia with Diffuse Spinal-cord Lesion, with Postmortem Findings." These two papers were discussed by Drs. Putnam, Osler, McPhedran, Shattuck, Musser, and Billings.

Dr. D. D. Stewart read a paper entitled "Acute Miliary Tuberculosis, Primarily Splenic."

Dr. Musser read a paper entitled "Notes on the Relapsing Fever of Hodgkin's Disease," which was discussed by Dr. Welch.

Dr. Stengel read for Drs. White and Pepper a paper entitled "A Study of Granular Degeneration of the Erythrocyte," which was discussed by Drs. Jacobi, Stewart, Peabody, and Stengel.

Dr. M. A. Starr read a paper entitled "The Toxic Origin of Neurasthenia and Melancholia."

Dr. W. W. Johnston presented a patient, formerly shown to the Association, suffering from Addison's disease.

Dr. W. W. Johnston read a paper entitled "The Evils Arising from Failure to Recognize the True Nature of Neurasthenia, and Some Causes of this Failure." The papers of Drs. Starr and Johnston were discussed by Drs. Cabot, Putnam, Herter, Baumgarten, and Starr.

Dr. Herter read a paper entitled "The Acid Intoxication of Diabetes and its Relation to Prognosis."

Dr. Joslin, by invitation, read a paper entitled "Metabolism in Diabetic Coma, with Especial Reference to Acid Intoxication." These two papers were discussed by Drs. Vaughan, Herter, and Pfaff.

Dr. Adami read a paper entitled "Classification of the Intoxications from a Pathologic Point of View."

Adjourned at 6 P.M.

Evening Session.

The Association was called to order at 8.15 P.M. by President Welch.

This session was devoted entirely to lantern-slide and microscopic demonstrations, without discussion.

Dr. Bond demonstrated "Some Features of Photomicrography."

Dr. Councilman demonstrated "The Renal Lesions in Diphtheria."

Dr. Ernst demonstrated "Some Lantern Slides."

Dr. Flexner demonstrated "Specimens of Experimental Acute Pancreatitis."

Dr. Welch, for Dr. Opie, demonstrated "Specimens of Hemorrhagic

Pancreatitis, Human and Experimental, and of Filarial Lymphatic Varix."

Dr. Welch, for Drs. MacCallum and Buckley, demonstrated "Specimens of Multiple Myelomata and of Epizootic Hemorrhagic Encephalitis."

Adjourned at 9.50 P.M.

WEDNESDAY, MAY 1ST—MORNING SESSION.

The Association was called to order at 10.05 A.M. by President Welch.

The following nominees, recommended by the Council, were elected to membership in the Association:

Dr. C. L. Greene, of St. Paul; Dr. William T. Howard, Jr., of Cleveland; Dr. George Blumer, of Albany; Dr. A. S. Warthin, of Ann Arbor; Dr. J. J. Kinyoun, of United States Marine Hospital Corps; Dr. E. K. Dunham, of New York; Dr. J. L. Morse, of Boston; Dr. H. Jackson, of Boston; Dr. A. R. Edwards, of Chicago; Dr. H. U. Williams, of Buffalo.

On recommendation of the Council, Dr. Charles F. Folsom, of Boston, was elected to honorary membership in the Association.

A discussion was held on "Bubonic Plague, Based upon the Outbreak in San Francisco." Dr. Barker discussed its "Clinical Aspects," Dr. Novy discussed its "Bacteriology," and Dr. Flexner discussed its "Pathology." The discussion was continued by Drs. Sternberg, Park, Shattuck, Vaughan, Dock, and Barker.

Dr. Reed read a paper entitled "Experimental Yellow Fever," which was discussed by Dr. Sternberg.

Dr. Ewing read a paper entitled "A Case of Malarial Nephritis, with Massing of the Parasites in the Kidney."

Dr. James read a paper entitled "Septic Infection Through the Stomach and Duodenum," which was discussed by Drs. Cabot, Meltzer, Kianicutt, and James.

Dr. Musser read a paper entitled "Two Cases of Streptothrical Infection: first, Bronchopneumonia; second, Abscess of the Brain," which was discussed by Drs. Abbott and Flexner.

Dr. McPhedran presented a "Specimen of Blue Urine."

Dr. Trudeau demonstrated a "Product of Bacillus Pyocyaneus Resembling Vegetable Gum."

Dr. Vaughan presented an abstract of his paper on "The Toxin of the Colon Bacillus."

Adjourned at 1.30 P.M.

Afternoon Session.

The Association was called to order at 2.40 P.M. by Vice-President Walcott.

Dr. Park read a paper entitled "To What Extent is Urine a Suitable Soil for Bacterial Growth?"

Dr. Kinnicutt read a paper entitled "Orchitis Complicating Typhoid Fever," which was discussed by Drs. Osler, Shattuck, Musser, Williams, and Baumgarten.

Dr. Williams read a paper entitled "Notes on the Treatment of Some Forms of Cancer by the X-Rays," which was discussed by Drs. Bond, Peabody, and Williams.

Dr. Packard read a paper entitled "Osteitis Deformans."

Dr. Osler read a paper entitled "The Spinal Form of Arthritis Deformans."

Dr. Stockton exhibited a "Skeleton of the Spinal Form of Arthritis Deformans."

Dr. Lamb, by invitation, exhibited "Skeletons of the Spinal Form of Arthritis Deformans." These papers were discussed by Drs. Sachs, Griffith, Cabot, Putnam, and Packard.

Dr. Sachs read a paper entitled "Certain Trophoneuroses and their Relation to Vascular Disease of the Extremities," which was discussed by Drs. Janeway, Osler, Putnam, and Sachs.

Dr. Stewart read a paper entitled "A Case of Subcortical Glioma of the Lower Part of the Ascending Frontal Convolutions: A Contribution to the Nature of the Speech Disturbance Arising from Lesions in this Situation."

Dr. Putnam read a paper entitled "Personal Experiences in Cases of Jacksonian Epilepsy, with Special Reference to the Question of Treatment by Operation;" discussed by Drs. Jacobi, Sachs, and Putnam.

Dr. J. K. Mitchell read a paper entitled "Clinical, Physiologic, and Chemical Studies of three Cases of Family Periodic Paralysis," which was discussed by Drs. Putnam, Meltzer, Mitchell, and Jacobi.

Dr. Forchheimer read a paper entitled "The Heredity of Appendicitis," which was discussed by Drs. Blackader and Forchheimer.

Adjourned at 6.05 P.M.

Thursday, May 2d—Morning Session.

The Association was called to order at 10 A.M. by President Welch.

The Secretary read the list of officers recommended for election by the Councillors.

Dr. Pfaff read a paper entitled "Some Observations Made in a Case of Diverticulum of the Esophagus," which was discussed by Dr. Meltzer.

Dr. Trudeau read a paper entitled "The Importance of a Recognition of the Significance of Early Tuberculosis in its Relation to Treatment," which was discussed by Drs. McPhedran, Jacobi, and Trudeau.

Dr. Adami read a paper entitled "A Study of a Series of Cases of Burns," which was discussed by Drs. Flexner, Jacobi, Welch, and Adami.

Dr. Meltzer read a paper entitled "Hemolysis."

During the meeting the following papers were read by title:

"Slow Pulse, with Special Reference to Stokes-Adams Disease," by R. T. Edes. "A Case of Acute Leukemia Presenting Some Interesting Features," by D. D. Stewart. "Sarcosporidia of the Mouse (Sarcocystis Muris) Transmitted Directly by Feeding Muscular Tissue," by T. Smith. "The Relative Prevalence of Bright's Disease in New York, London, and Berlin," by H. M. Biggs. "Lithemic or Recurrent Coryza," by B. K. Rachford. "A Further Report on a Case of Presystolic Mitral Murmur Associated with Systolic Tricuspid Murmur Complicating Pregnancy, Reported to the Association in May, 1899," by James Tyson. "The Extension of Aortic Aneurysms Into and Between the Walls of the Heart, and Dissecting Aneurysms of the Heart," by L. Hektoen. "A Study of Bacteria Isolated from Cases of Dysentery," by F. F. Wesbrook. "Report of a Case of Spondylosis Rhizomelia, with Autopsy," by C. L. Dana. "Observations on the Nature and Treatment of Pernicious Anemia," by A. McPhedran. "The Relation of the Tracheal Tug to Fixation and Elasticity of the Left Lung," by H. Sewall.

It was resolved that the Recorder be requested to have a complete index made to the TRANSACTIONS of the Association.

The following officers were elected:

President—James C. Wilson.
Vice-President—James Stewart.
Recorder—S. Solis Cohen.
Secretary—Henry Hun.
Treasurer—J. P. Crozer Griffith.
Councillors—Frank Billings and F. P. Kinnicutt.
Representative on the Executive Committee of the Congress of American Physicians and Surgeons—William Osler.
Alternate Representative—F. H. Williams.

On motion of Dr. McPhedran, it was resolved that the Secretary be instructed to present the thanks of the Association to the Cosmos Club and to the Arlington Hotel for furnishing rooms for the meeting.

On motion of Dr. Jacobi, it was resolved that the thanks and congratulations of the Association are due Dr. Welch for his labors, which have resulted in such a successful meeting of the Association.

Adjourned at 12 M.

HENRY HUN,
Secretary.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

AN UNDESCRIBED CARDIAC SOUND.

By H. A. HARE, M.D.,
OF PHILADELPHIA.

I AM not ignorant of the fact that in giving this title to the brief paper which I am about to present for your consideration I have had a certain amount of temerity, for the discussion of any physical sign at the present time that has not already been described is apparently impossible. There is no doubt in my mind that everyone here has heard this sound, and yet I am not familiar with any mention of it in books devoted to physical diagnosis or the practice of medicine. The title of my paper is, therefore, correct, even if it is not a new sound. The sound to which I refer is that peculiar vibrating sound occurring with systole and heard best in an area extending from one inch to the right of the sternum to one inch to the left of the nipple, on the nipple level, and which is sometimes so dry, if I may use such a term, that I have at times considered it somewhat like the pericardial friction-sound heard in pericarditis near the base. That it is not a friction-sound I am very confident, although I must admit that its cause is not clear. Personally, I believe it to be due to vibrations in the chordæ tendinæ produced by imperfect contraction of their muscular attachments, because I have never met with the sound except in cases of general debility with a feeble, irritable heart. So frequently have I met with this sound in cases of early pulmonary tuberculosis that I have come to regard it as indicative of this disease, and always search particularly closely for pulmonary signs if this cardiac sign is present. I do not think I have heard it frequently if at all in advanced phthisis, but I have very commonly heard it in the general systemic and cardiac feebleness of influenzal convalescence. It is emphatically not the hemic murmur of anemia either in the area of sound or in its character. The hemic murmur, so called, while it may be heard at the apex, is generally heard elsewhere, and is soft and purring, or blowing, while the sound I refer to is not a murmur in the ordinary sense,

but a vibratory sound resembling the sound "ching" at each systole. It is short and quick, not changed by deep or superficial pressure of the stethoscope, and is not entirely put aside by rest in many cases, although it is usually decreased by this means. It becomes accentuated by nervousness or fear, but not by exercise of a sufficiently violent kind to distinctly accentuate ordinary sounds. The sound "ching" first named does not quite represent the sound I refer to, being too metallic and not crisp enough, but I can find no word that represents it better. Sometimes it has a coin sound, and can be represented by the sound made by the school-boy who clasps his hands together, having a small air-space between the palms, and then strikes the back of one of the clasped hands on his knee in the endeavor to make a friend believe that he holds coins between the hands. This sound is not the musical murmur described by Dr. Da Costa in irritable heart, which resembles the "cooing of a pigeon," for it is not so clear and distinct. It is more like that caused by touching a stiffly starched cuff against the other while they are on the wrist, allowing them to rub slightly. The sound is usually heard in shallow chested persons who have a diffuse apex-beat with dilatation, actual or relative, and when the heart is speeding at about 100 to 120. I have never met with this sound in cases of ruptured compensation or in cases of fatty heart, nor is it the loud, accentuated, ringing sound met with in healthy hearts after exercise or due to excitement; nor, again, is it the conditon described by Dr. Da Costa as the "irritable heart of soldiers," or that by Allbutt, Seitz, or McLean. There are no subjective cardiac symptoms on the part of the patient, as a rule.

DISCUSSION.

DR. OSLER: There are two interesting sounds which you hear, either of which might be this new sound of Dr. Hare's. I think we all must have been impressed by the fact that frequently at the apex we hear a little grating sound much like a fine pericardial friction, yet it has not the rubbing nature of that sound. There is a distinct difference in the majority of healthy hearts between the first sound over the apex and that as you move toward the sternum, a more crunching sound, which is peculiar and remarkable. I do not know that I ever heard the sound Dr. Hare refers to unless it is one of those peculiar sounds that has sometimes worried and sometimes puzzled me.

RIGHT-SIDED CARDIAC HYDROTHORAX.

By ALFRED STENGEL, M.D.,
OF PHILADELPHIA.

My interest in the subject of unilateral and especially right-sided hydrothorax was occasioned by a succession of cases under my observation in 1893, at a time when I was collaborating in the preparation of some text-book articles on the subject of cardiac disease. I then had at one time under observation three cases of unilateral hydrothorax without external edema, and the difficulty in distinguishing such effusions from inflammatory pleural exudates led me to investigate the causes of the conditions. Subsequently another series of cases led me to invite Dr. J. Dutton Steele[1] to report them and publish our views regarding the causation of this one-sided nature of pleural dropsy.

Systematic writers, almost without exception, state that the effusion in heart disease is always bilateral. Occasionally, however, the statement is met with that it may be unilateral, and that it is more frequent on the right side than on the left. MacLean[2] quoted Home and reported a case of right-sided hydrothorax in a man, forty-five years of age, who was suffering from some form of tumor of the liver. He also referred to Hoffmann, who reported the same occurrence in a man of sixty years with enlargement of the liver. H. Kennedy[3] states that "in heart disease double pleural effusion occurs, though one side contains more fluid than the other. Hydrothorax on one side is the exception. As far as my observation has gone, when the effusion was single the right pleura was the one engaged." Subsequently, in 1868, Wintrich[4] states that hydrothorax is unilateral when the pleura of the other side is closed by adhesions, but very rarely is

[1] University Medical Magazine, May, 1897.
[2] On Hydrothorax, 1814.
[3] Dublin Journal of Medical Sciences, 1834, vol. xv. p. 236.
[4] Virchow's Handbuch der Path. u. Therap., vol. v. p. 366.

it one-sided, though the opposite pleura is normal. The right pleura was, in his experience, habitually the seat of the greater amount of liquid. In the course of his article he refers to a case (quoted quite fully in Steele's paper) in which there was a right unilateral effusion of considerable magnitude, without general edema and with no lesions excepting a fatty heart and liver. A most interesting case was reported by Pepper[1] of a man, aged seventy-one years, with right-sided hydrothorax. The effusion was tapped several times. In this case pleural adhesions were found on the left side. The case was additionally interesting from the existence of cirrhosis of the liver.

Since the publication of Steele's paper I have repeatedly observed the same characteristic disposition of the effusion, and have made further observations of the anatomic relations at autopsies, as well as in the anatomic subject, as a result of which I feel more thoroughly satisfied with the soundness of the view which Dr. Steele and I held and which he published in his paper. To determine the frequency of hydrothorax and the conditions of its occurrence, I have analyzed a hundred consecutive cases of cardiac disease that have been under my observation in the University Hospital, and in which sufficient clinical or pathologic information was preserved to make the notes of value for my present purposes.

These 100 cases included 17 in which the clinical or pathologic evidence proved the existence of hydrothorax. This proportion contrasts strongly with that obtained by Steele in his analysis of the autopsy records in the Middlesex Hospital and the Philadelphia Hospital. Among a total of 2427 autopsies, 173 were cardiac cases in a strict sense,[2] and of these 75 were complicated with hydrothorax; but this series, it is to be noted, consists of fatal cases of cardiac disease, while mine includes only a minority of fatal ones.

Of the 17 cases in my series of cases, 5 were instances of effusion on the right side only (the evidence of effusion in one of the 5 being somewhat questionable); 3 were cases of left-sided effusion, in 2 of which the right pleura was found entirely obliterated at autopsy, and in the third there was a suspicion of an aneurysm in the left chest; 9 cases had bilateral effusion at some stage—2 of these were first right-sided, then bilateral, with less extensive effusion on the left side; in

[1] Philadelphia Medical Times, 1872-1873, vol. iii. p. 560.
[2] Only cases of chronic myocardial or valvular diseases were included.

the other 7 the effusion was bilateral from the beginning, but the right side was particularly affected. Condensing these figures, we find that the effusion was at some time confined to the right side in 7, was bilateral with greater involvement of the right side in 7, and was left-sided in 3. These figures show even a greater preference of hydrothorax for the right side than did the statistics of Steele, and warrant the statement that the distribution is not an accidental one.

DISTRIBUTION OF FLUID.

Unilateral, right	5
Unilateral, left	3[1]
Unilateral, right; followed by slighter left pleural effusion	2
Bilateral, right effusion predominating	7
Total	17

When we come to consider the etiology of hydrothorax, a retrospect of the causes of dropsical effusion is in place. Obstructions of the venous circulation by causing stasis and increased intravenous pressure take the first place; next in importance is lymphatic obstruction, with consequent accumulation of the normal extravasates; a third condition is the state of the perivascular tissues; this operates by reducing tissue tone, and thus lessening the barrier to extravasation, as, for example, when a chronic inflammatory condition of the serosa of the pleura or peritoneum occasions excessive leakage; a fourth and relatively unimportant condition is hydremia or anemia.

When my attention was first directed to unilateral hydrothorax without external edema, it seemed likely that an old pleural inflammation on the affected side had so altered the perivascular tissues that subsequently serous extravasation occurred with general venous stasis that had not become sufficient to cause external or bilateral pleural edema. This view was supported by the observations of Piazza-Martini, Lizzato, Cardanelli, Villani, Pepper, Howe, and Hoffmann, who recorded cases of right-sided hydrothorax in association with hepatic cirrhosis and other hepatic diseases; and by the suggestion of Villani and Pepper that irritations or inflammations of the liver may extend through the diaphragm to the pleura, and thus occasion a combined pleural exudate and transudate. The regular occurrence, however, of hydrothorax on the right side without any manifest or

[1] In one possibly aneurysm in left chest; in the other two total obliteration of right pleura.

probable disease of the liver made this explanation improbable. It seemed, then, that some anatomic condition was to be sought, and two suggestions offer themselves: either the obstruction of the circulation in the superior vena cava causes obstruction of the outflow of the right lymphatic duct and consequent accumulation of serous liquid, or the venous circulation in the intercostal and right bronchial veins entering the vena azygos major is obstructed, and excessive venous transudation causes the unilateral hydrothorax. The former view is unlikely, because the right lymphatic duct is quite effectually protected by valves, and for the reason that in case this were the cause of the hydrothorax, unilateral swelling of the arm, neck, and chest of the right side would of necessity be more frequent. It has occurred to me that a study of the specific gravity of the fluid might throw some light upon the cause of the effusion. *A priori* an effusion due to lymphatic obstruction and accumulation of the normal transudates ought to have a higher specific gravity than that of a transudate due to venous obstruction; but statistics do not substantiate this view. Thus the ascitic fluid in cases of tumors of the receptaculum chyli has been found by various observers: 1009 (Bargabuhr), 1007 and 1012 (Leybecker), 1008 (Unger), 1010 (Hektoen), 1014 (Schram), 1014 (Renvers), and 1011 and 1015 (Senator). These figures agree quite closely with those obtained in hydrothorax or hepatic ascites, and negative our expectations, though, as Ribbert observes, the conditions of lymph formation are so altered by obstruction of a main channel that the composition of the lymph varies from the normal. Without this confirmation, however, the other reasons given seem to me sufficient to indicate that obstruction of the right lymphatic duct is not the operative cause.

Before considering the question of venous obstruction it is of interest to note the varieties of cardiac disease in which right-sided hydrothorax has occurred.

TABLE OF ONE HUNDRED CONSECUTIVE CASES OF CHRONIC HEART DISEASE.

1. Mitral valve alone affected:		
Mitral regurgitation	27	
Mitral stenosis and regurgitation	8	
Mitral (unspecified)	8	
Mitral stenosis	6	
Total	—	49

2. Aortic valve alone affected:		
Aortic stenosis and regurgitation	10	
Aortic regurgitation	5	
Aortic valve disease	2	
Total	—	17
3. Aortic and mitral disease		13
4. Myocardial disease (fibroid, fatty, and dilated)		13
5. Aortic, mitral, and tricuspid disease		4
6. Mitral and tricuspid disease		4
Grand total		100

TABLE OF SEVENTEEN CASES OF HEART DISEASE ATTENDED WITH HYDROTHORAX.

1. Mitral valve alone affected:		
Mitral regurgitation	5	
Mitral stenosis and regurgitation	2	
Mitral stenosis	1	
Total	—	8
2. Aortic and mitral disease		4
3. Aortic, mitral, and tricuspid disease		3
4. Myocardial disease		2
Grand total		17

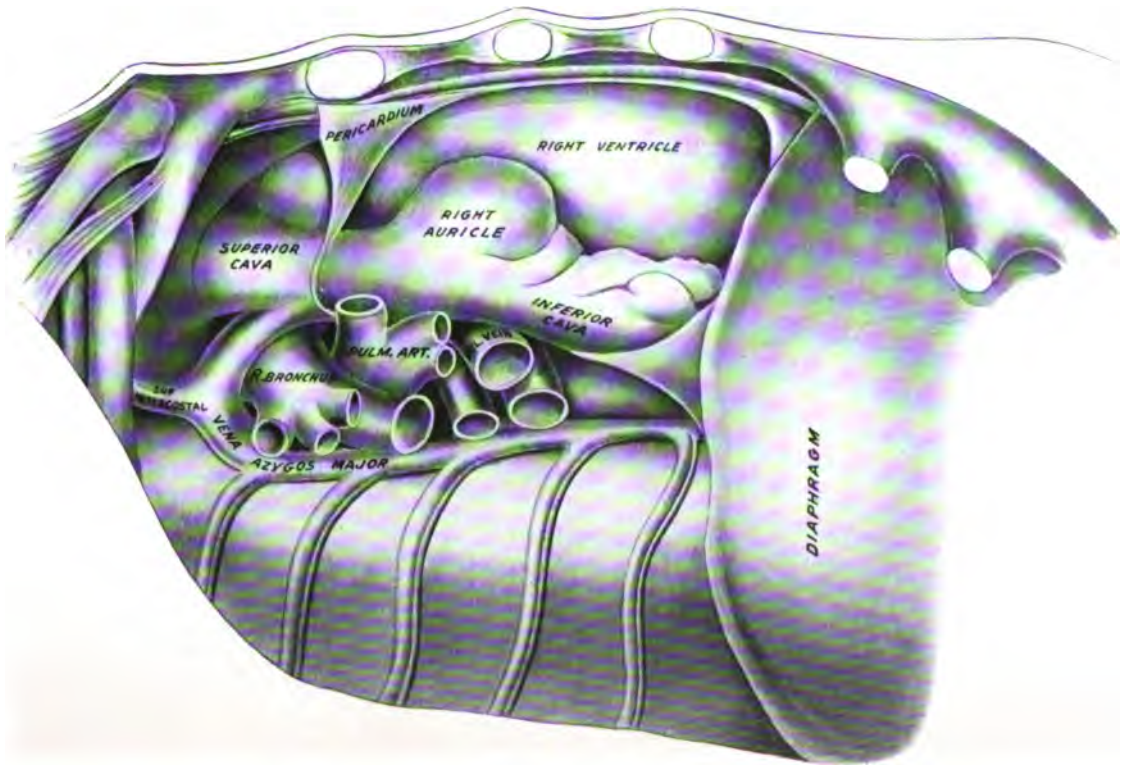
In the entire series of cases analyzed there was clinical or pathologic evidence of mitral disease in 70 per cent. of the cases, and of tricuspid disease in 8 per cent.; in the series of 17 cases with hydrothorax, the mitral valve was affected in 88 per cent. of the cases and the tricuspid in 17 per cent. While both series are so small that great weight cannot be laid upon the figures given, especially as it is likely from general considerations that mitral disease (primary or secondary) is always present when dropsies set in, some value at least attaches to the fact that in all cases in which right-sided hydrothorax had occurred there was considerable enlargement of the right heart. Much more important indications were met with in two autopsies in which unusual dilatation of the right ventricle, auricle, and venæ cavæ, and marked backward pressure upon the root of the right lung and azygos vein were discovered. Taking these facts in connection with anatomic studies, it is evident that the pressure here indicated is the cause of the sole or predominating effusion in the right side. Though I had reached this opinion independently, it had been previ-

ously expressed by others. Jaccoud,[1] while discussing the etiology of right-sided hydrothorax in cases of tumors, etc., as well as in heart disease, suggests pressure upon the azygos vein and superior vena cava as the cause; and Piazza-Martini believes that the effusion in cirrhosis of the liver is due to pressure on the azygos vein by dilated esophageal veins. A study of the anatomic relations of the azygos vein, as seen in the accompanying drawing, shows its close relations to the inferior vena cava and right auricle below and to the bronchus and vessels of the root of the right lung above. Even a moderate dilatation of the auricle and cavæ must of necessity exercise considerable compression upon the azygos vein, and thus reduce its lumen. On the left side conditions are very different. The higher position of the left auricle prevents compression of the lower azygos vein, which receives the intercostal veins up to the sixth or seventh interspaces, and then empties into the major azygos after crossing the vertebral column. The upper left azygos vein drains but one or two intercostal spaces, and is so placed as to be little likely to be compressed. The left superior intercostal vein is quite out of reach of compression and its flow is upward, so that even a compression of its lower part could have little effect. These facts show the readiness with which dropsical effusions of the right chest may be occasioned by dilatation of the right auricle with direct and indirect pressure (the latter by displacement of the root of the right lung) of the major azygos vein.

The secondary and less extensive effusion in the left chest is explained by the fact that the lower and upper azygos veins of the left side discharge into the major azygos. Obstruction of the last-named vessel would therefore occasion immediate and complete venous stasis in the right chest and secondary stasis in the lower portions of the left chest. The anatomic conditions, then, bear out completely the clinical observations.

Finally, a point of practical interest needs consideration. Though most authors state without reservation that inflammatory pleural effusion is distinguishable from hydrothorax by its unilateral character, the preliminary symptoms and the fever, some, as Leube, Pepper, and Osler, have very properly insisted that hydrothorax may be

[1] Traite de Pathologie Interne.



Relations of parts as viewed from the right.

unilateral and unattended by external edema; and, on the other hand, inflammatory pleural effusion may be latent—that is, unaccompanied by the usual symptoms. A knowledge, then, of the possibility of hydrothorax of this character is of clinical importance, though, even with the full recognition of this possibility, difficulty may occasionally arise in determining whether an effusion is dropsical or inflammatory. This difficulty was met with in Case I. of my series, but happily the difficulty is rare and hardly ever insuperable. In some cases a unilateral hydrothorax is chronic in character, and the fluid after repeated tapping increases in specific gravity as in Case I. In such instances it may be that a secondary inflammatory exudation has been added to the dropsical effusion.

Summary of Cases.

Case I.—J. M., aged thirty-three years, had suffered with severe pain at the lower part of the thorax six weeks prior to admission. He had noted, however, an increasing rapidity of heart action and a tendency to palpitation for a year prior to the onset of this trouble. After the attack of pain, which passed from one side of the chest to the other, he suffered with palpitation, spasmodic dyspnea, and great weakness, but after some days he improved and resumed his work. Two weeks later there was a recurrence of the trouble, and after that he was compelled to discontinue his work.

When admitted to the hospital there was evidence of fluid in the right chest. The right apex was rather hyperresonant, and this note was found as far down as the fifth interspace in the recumbent posture. In the sitting posture the level of dulness rose three-fourths of an inch. The level of dulness was higher in the axilla than at the front or back. The left chest was hyperresonant throughout the normal pulmonary limits. The heart-sounds were extremely irregular and rapid; the fetal rhythm was sometimes present, but the sounds were not especially valvular in character. At the aortic cartilage the sounds were heard with great difficulty.

The subsequent history of the patient in the hospital showed evidence of a primary cardiac lesion.

A month after his admission the right chest was aspirated and seventy-two ounces of clear, serous liquid was removed. The specific gravity of the liquid was 1010. There was a small number of leukocytes and red blood-cells. Subsequently distinct evidences of mitral regurgitation were obtained and the fluid in the chest disappeared. Later attacks of delirium cordis and evidences of mitral stenosis, as well as regurgitation, appeared.

After leaving the hospital he was readmitted with swelling of the feet and a reaccumulation of liquid in the right pleural cavity. The liquid this time extended as far as the third interspace; sixty-two ounces of liquid, specific

gravity 1017, were removed. The patient eventually recovered compensation and was discharged.

CASE II.—Ed. M., aged seventy-two years, a miller, was admitted to the hospital complaining of shortness of breath of several years' duration. There was also palpitation of the heart and edema of the lungs.

Physical examination showed the signs of general atheroma, with aortic and mitral disease and tricuspid regurgitation. There was a loud, rasping, double murmur at the aortic region, and a softer, systolic murmur at the apex, which was transmitted outward. At the ensiform there was a superficial systolic murmur, which faded in intensity toward the apex. The right chest was flat from the third rib downward.

Tapping of the abdomen removed two and one-half quarts of liquid and subsequently two quarts of clear, yellow serum. The patient finally developed Cheyne-Stokes breathing and died. No autopsy.

CASE III.—Chas. R., aged thirty-three years, a packer, had been subjected in his occupation to very hard labor. His illness began after taking cold a few months prior to admission. Shortness of breath, and later swelling of the feet and legs, were the prominent symptoms. He was admitted with some dyspnea and great swelling of the legs. The heart action was extremely irregular, but no murmur could be detected. Dulness was found over the bases of both lungs, more marked on the right side. The edema increased. Fluid in the right chest was afterward discovered and aspiration was practised. Thirty-five ounces of clear, straw-colored fluid were drawn off. The specific gravity of this was 1010. There was considerable relief and steady improvement, but there was still fluid in both sides of the chest, the note reading: "Dulness extends about half-way up the chest posteriorly on the left side and about two-thirds up over the right."

CASE IV.—J. G., aged fifty-two years, a hostler, had had dropsy when a child, but recovered completely. He had been a hard drinker. He had rheumatism two years before, the attack lasting two months. He had suffered from palpitation, and the winter previous to his admission had swelling of his hands and feet, with shortness of breath.

When admitted he had extreme dyspnea. The heart-sounds were very irregular and weak, and a systolic mitral murmur was discovered. There was no albumin in the urine, nor any other signs of renal disease. The legs were tensely distended with dropsical infiltration. There was slight dulness at the bases of both lungs. He suffered with repeated attacks of intense dyspnea, and finally he died suddenly in one of these attacks.

At the autopsy there was found slight aortic valvular thickening. The mitral valve and ring seemed normal. The right ventricle was greatly dilated. The right auricle and the vena cava were also greatly dilated. The weight of the heart was 560 grams. The right pleural cavity was one-half full of serum, the left one-quarter full. The lungs showed some emphysema, chronic bronchitis, and areas of atelectasis. The liver weighed 2100 grams.

CASE V.—William A., aged twenty-five years, a coal miner, had an attack of rheumatism six months before, and after this never completely recovered his health. He had rheumatic pains in the joints and uncomfortable feelings about his heart. Occasionally there were severe palpitations. There was never edema of the feet or hands. The fingers were club-shaped at the ends.

Physical Examination. At the first examination aortic regurgitation, with mitral stenosis and regurgitation, was found. The lungs were reported normal. There was no edema.

A month later the note reads: "Crackling and some dulness at right base posteriorly, probably indicative of edema." Two months later: "There is evidence of increasing edema at the base of the right lung, as indicated by greater dyspnea, dulness, crackling, and frothy expectoration."

Later there was noted impairment of resonance below the scapula, a little more marked on the right side. A month later there was decided evidence of edema at both bases, then "dulness at bases, with absence of breath-sounds." Soon after this the patient succumbed.

CASE VI.—Sarah R., aged twenty-two years, had begun to suffer with swelling of the feet two years before admission and a little while after the birth of her last child. Later she had shortness of breath, palpitation, and loss of strength. The urine grew more scanty, and the symptoms exaggerated about a year before she came under observation.

At that time the abdomen was swollen and she was tapped three times. There was never any edema of the hands or face. When admitted she was cyanotic and subicteroid. The legs were edematous to above the knees. The abdomen was greatly increased in size. There were distinct evidences of advanced mitral valve disease (stenosis and regurgitation). The right heart was greatly enlarged. Tne abdomen contained fluid. There was dulness at the right base posteriorly and below the mid-scapula, with bronchial breathing and increased fremitus and resonance in the upper half of the dull area, while below the breath-sounds were weak and fremitus was absent. The vocal resonance in this situation was egophonic. The abdomen was tapped and ten quarts of clear fluid were removed. The liver was then easily felt and was evidently diseased. The patient improved steadily. Later a note reads: "There is dulness at both bases posteriorly, reaching to the lower third of the scapula on the right side and one and one-half inches lower on the left."

CASE VII.—Henry B., aged forty-seven years, after exposure a year before admission, suffered with cough, dyspnea, and some swelling of the feet. Several similar attacks occurred during the intervening year, and he was admitted to the hospital with about the same condition. The dyspnea was quite marked, and there was decided edema of the extremities and body. On percussion over the chest there was found some increased dulness posteriorly on the left side, which shifted on motion, and a similar shifting dulness on the right side in the axillary line. (The extent of the dulness is not

stated.) There was a systolic followed by a diastolic murmur at the apex, and a loud double murmur at the aortic region.

It seems from the statements that on the left side there was shifting dulness behind, and on the right side there was similar shifting dulness in the axillary line, that there was more fluid on the right than on the left, but it is not explicitly stated here or elsewhere in the notes of the case.

CASE VIII.—Sarah C., aged sixty-four years, was admitted, having dyspnea and some swelling of the feet. The history indicated that the trouble had followed an attack of rheumatism two years before. There were some cyanosis and icterus, and moderate external edema.

An examination showed a well-developed cardiac disease, with extension of the dulness three-quarters of an inch beyond the mid-clavicular line and one inch and a quarter to the right of the sternum. There was a well-marked mitral regurgitation. The pulmonary percussion signs were good, being rather hyperresonant except at the bases, where there was slight dulness. The breath-sounds were unaltered, except at the base of the right lung, where the breathing was weak and accompanied by crackling râles. Subsequently it was noted that "there is little dulness over the right base, while fremitus and breath-sounds are weak." Later, "there are still signs of effusion of liquid at both bases, reaching higher—to the lower third of the scapula—on the right side." Subsequently the note reads: "The right pleura now seems free of fluid."

CASE IX.—L. C., aged sixty-nine years, a lumberman, had suffered with rheumatism during the last six years, and had lived a life of much exposure. He became troubled with shortness of breath and precordial pain. He had been losing flesh and strength, and his legs had been edematous several times. When admitted he was extremely dyspneic and slightly cyanosed. The peripheral arteries were atheromatous. Examination revealed dulness below the fourth interspace on the right side, and from this point downward to an inch and a half below the costal margin. Posteriorly dulness began at the angle of the scapula, and the breath-sounds as well as the vocal fremitus were greatly weakened in the same situation. The heart was greatly enlarged, both to the right and to the left. The auscultatory sounds were those of mitral regurgitation. There was a suspicious wave of fluctuation in the abdomen, but no edema of legs. He improved somewhat, but the dulness at the right base persisted, and after some days bronchial breathing and increased fremitus were found at the right base. Later, dulness along the sternal border of right scapula was noted. This afterward disappeared, and the percussion note became the same on the two sides. In a subsequent note reference is made to flatness posteriorly and laterally on both sides. The upper and interior borders of the flatness moved with change of position. The degree of effusion on either side is not mentioned.

CASE X.—Joshua E., aged fifty-six years, a laborer, had rheumatism twenty-five years before and an occasional slight attack since. He had used alcohol very freely. His cardiac history began in an attack of rheumatism

six years before admission. When admitted he had dyspnea, swelling of the ankles, some abdominal swelling, which had begun three weeks before. The apex-beat was very extensive, stretching from the sixth rib up to the fourth interspace. The cardiac dulness extended beyond the mammary line on the left side, but only to the mid-sternum on the right. A soft systolic murmur was heard at the apex and transmitted as far as the axillary line. A loud blowing, systolic murmur was heard at the aortic cartilage. The second sound was clear and ringing. The hepatic dulness is reported as beginning at the fourth interspace and extending to the border of the ribs.

No definite statement of effusion in either chest is made, but the intimation in the reference to the hepatic dulness of an effusion seems to be sufficiently marked to merit notice.

CASE XI.—O. D., aged forty years, a miner, had been well up to two years before, when he began to run down in weight and in strength. He had used alcohol freely. He became dyspneic, and suffered with an increase of a chronic cough. The dyspnea seemed rather paroxysmal. There was never any swelling of his feet. When admitted there was found enlargement of the superficial veins and of the superficial lymphatic glands. There was impairment of the pulmonary resonance in various situations. The pulmonary sounds suggested more or less consolidation of the lung. His heart was seemingly decreased in size, and no definite disease could be determined. The sound at the apex was on one occasion most peculiar, having a gurgling and churning character of such peculiar confusion that a pyopneumopericardium was suspected. The first sound itself was so loud and metallic that the cliquement metallique was suggested. These sounds were heard a little below the usual apex region, and extended toward the right as far as the sternum. At the base of the heart and in the pulmonary region the second sound was harsh and quite murmurish. At the aortic region the sounds were weak. The subsequent history of the case gives no evidence of importance in connection with the subject in hand.

At the autopsy the left pleura was adherent over the upper two-thirds, the right over the upper third. Below, on the right side, there was a moderate effusion. Adhesions between the pleura and pericardium on both sides were more marked on the left. Within the pericardium no evidence of recent inflammation, but some milk spots on the left ventricle and right auricle. The heart was greatly enlarged, principally on the right side. The muscle was flabby and pale. There was no endocarditis, old or recent, but the walls were somewhat thickened. The left cavities of the mitral orifice were a little dilated. The right cavities of the tricuspid orifice were dilated to an extreme degree. The lungs were absolutely solid, with evenly distributed coal-dust deposit. The liver was congested and fatty, but not much enlarged. The spleen was congested and indurated.

CASE XII.—John T., aged forty-four years, a machinist, had always been a strong, robust man of good habits. A year and a half before he had been confined to bed with influenza, and at the same time suffered with a sensa-

tion of weight on his chest and difficulty in breathing. The sensation came on in paroxysms lasting a couple of hours, and they had grown more frequent and more severe until he suffered practically constant dyspnea. Occasionally he had been confined to bed for weeks at a time. There was no sign of edema. The heart was slightly enlarged, and there seemed to be a presystolic mitral murmur, with an aortic regurgitant murmur. The notes state vaguely that "there was an area of dulness over the base of the heart, in which there is neither thrill, pulsation, nor murmur." The left pulse seemed retarded and of less force than the right. The pupils were equal, but there was slight suprasternal pulsation. The treatment recommended was potassium iodide and tincture of lobelia in brown mixture. A subsequent note reads: "Over the left base below the sixth rib is an area of movable dulness, over which the tactile fremitus is almost lost and the breath-sounds and vocal resonances are nearly absent. There is no murmur to-day." There seemed to have been a suspicion at that time that this case was one of aneurism, but the notes that have been preserved are meagre, as the chart to which reference is made and which contains the details has been lost.

CASE XIII.—G. V. C., a woman of twenty years, whose family history was good, stated that she had been healthy until about twelve years of age, but at that time grew very rapidly and was not strong. She was very tall and thin, and continued weak until about nineteen. At twenty-one she had bronchopneumonia, lasting nearly all the winter. Two years later she had double pneumonia for three weeks, but made a good recovery. Two and a half years before she came under observation, after the birth of her second child, she suffered with palpitations of the heart and severe pains, which made breathing difficult. At the end of two months she recovered sufficient health to leave her bed, but her feet swelled and general dropsy resulted. There was severe dyspnea, and fluid was discovered in the right pleural cavity, which required aspiration four times, and in the abdominal cavity requiring aspiration once. No aspiration was necessary after that time. When she came under observation there was no sign of renal disease, but well-marked evidences of mitral stenosis and some ascites. The latter subsided under medical treatment.

CASE XIV.—M. C., a man, aged forty-five years, had had no severe illnesses, but had used alcohol to excess. He had been troubled with frequency of urination. Two weeks before admission he developed a cough and dyspnea. There was no expectoration. The symptoms grew in severity, and after a few days were followed by swelling of the face, then of the feet and legs. The temperature on admission was 99.2°, the pulse 84, the respirations 28; there was marked edema of the legs and feet and slight cyanosis. The expansion of the lungs was restricted, especially upon the left side. There was impairment in resonance at the right base below the angle of the scapula, and below the middle of the scapula on the left side. Fremitus and breath-sounds were almost lost over these affected areas. The cardiac apex was scarcely palpable; the dulness extended from the second rib on the left to

the sixth rib below, and from one and one-half inches to the right of the sternum and to the left as far as the mid-clavicular line. There was a slight systolic apical murmur, not distinctly transmitted, and a decided accentuation of the pulmonary sound. The pulse was of good volume, but soft; there were slight movable dulness and fluctuation in the abdomen. The patient improved for a time, but subsequently grew worse, and died in the hospital.

The necropsy showed: edema of the lungs, obliterative pleurisy of the right pleural cavity, pleural effusion in the left side, slight ascites, and chronic parenchymatous nephritis (glomerulitis). There was a recent rupture of the internal coats of the aorta about two inches above the bifurcation, which was explained by the severe paroxysms of coughing to which he had been subject. The heart was hypertrophied; the aortic valves had but two segments.

CASE XV.—P. K., aged forty years, a miner, was admitted August 25, 1899. No history was obtainable, as the patient did not speak English. There was edema of the face, a subicteroid hue of the conjunctiva, and tympanitic distention of the abdomen; the legs and feet were also edematous. The superficial arteries pulsated, and the pulse was of the Corrigan type. The physical examination showed great hypertrophy, the apex being in the fifth and sixth interspaces, an inch outside the mid-clavicular line. The right border extended considerably beyond the right border of the sternum. There was a double murmur at the aortic area, with the usual transmission of the stenotic and regurgitant aortic murmurs. At the mitral area was heard a systolic murmur and a presystolic rumbling sound, which was regarded as a Flint murmur. Examination of the lungs showed some flatness at both bases, but the breath-sounds were heard at the right base and inaudible at the left, and the flatness at the left base was movable and extended higher, reaching the fourth rib in the sitting posture.

The amount of the edema changed from time to time and the patient's condition fluctuated. He died suddenly, October 2, 1899.

The autopsy showed the following conditions: Old adhesions binding the right lung to the chest wall; considerable left-sided hydrothorax, with compression of the lower lobe of the left lung, pericardial effusion. The heart was enlarged, the walls considerably hypertrophied and further thickened by deposition of fat. The mitral valve seemed normal in appearance, save for a slight thickening at the edges; the aortic valve was considerably diseased, the segments being thickened and retracted. There were atheromatous nodules in the intima of the aorta. The tricuspid orifice was considerably dilated and was regarded as decidedly insufficient.

CASE XVI.—Samuel T., aged seventy-one years, a gardener, had been a man of good habits. He was admitted November 13, 1899, stating that he had suffered with left-sided pneumonia during the previous February. He was confined to bed four weeks and had much dyspnea and swelling of the feet and legs. He recovered from this condition and was able to work dur-

ing the summer, but took a "cold," and again became very short of breath and grew dropsical. He also suffered with pain and fulness in the epigastrium and had a slight cough, and during three weeks before his admission he was confined to bed. He was an emaciated old man, with atheromatous facies, slight cyanosis, and marked general edema. His pulse was small and compressible; the apex-beat was weak and diffuse. The heart was increased in size, extending 3 cm. beyond the left mammary line and a little beyond the right border of the sternum. There was a soft systolic murmur at the apex and an accentuated, reduplicated second pulmonary sound. The apical murmur was transmitted into the axilla; there was flatness at the right base below the fifth rib in the recumbent posture, and the fourth rib when sitting upright. Posteriorly, flatness began at the angle of the scapula. Later, the effusion on the right side was more marked, and slight effusion in the left chest was noted. The patient improved steadily and was finally discharged well.

CASE XVII.—A. L., a negress, aged fifteen years, was admitted September 13, 1889. She had had typhoid fever in 1898, and had remained more or less ill since that time. Her chief complaints were of pains about the heart and shortness of breath, and finally the feet and abdomen began to swell. There was no history of rheumatism or scarlet fever.

On admission there were decided dyspnea, distention of the veins of the neck, and positive venous pulsation. The abdomen was greatly distended and the hepatic region swollen. The apex-beat was displaced to the left, being palpable in the anterior axillary line in the sixth interspace. There was decided movable dulness in the right and left chest, the upper level being at the angle of the scapula on the right side and an inch lower on the left. The heart dulness extended from the third rib above and from a line an inch and a half beyond the right border of the sternum, on the right to the anterior axillary line on the left. There was a loud systolic mitral murmur and an accentuated pulmonary sound. The lower edge of the liver was felt as low as the level of the umbilicus. There was effusion in the chest with fluctuation. Under treatment the conditions rapidly improved.

Number and name.	Diagnosis	Pleural involvement.	Specific gravity.	External edema.	Condition of liver.	Pleural adhesions.	Remarks.
1. J. M.	Mitral regurgitation and stenosis.	Right.	1010, later 1017; 372 later, 362 tapp'd	Some time after hydrothorax.	.....	.....	Possibly associated pleurisy and hydrothorax.
2. E. M.	Aortic mitral and tricuspid regurgitation.	Right.	Tapped twice.	None	.....	.....	Edema of lungs and dyspnea; no evidences of pleurisy.
3. C. R.	Myocarditis (fibroid).	Right; later both.	1010; 335 by tapping.	Extensive.			
4. J. G.	Aortic mitral and tricuspid.	Right ½ full, left ¼ " at autopsy.	.....	Extensive.	Wt. 2100 g. congest'd	None.	
5. W. A.	Aortic and double mitral.	Dulness at bases, especially right, supposed to be liquid.	.....	None.			
6. S. R.	Double mitral.	Dulness at bases with absent fremitus, more on right.	.....	Considerable; also ascites.	Palpable after tapping; cirrhotic.		
7. H. B.	Aortic and mitral.	Both sides; more on right	.....	Considerable.			
8. S. C.	Mitral regurgitation.	Both sides; more on right	.....	Slight.			
9. L. C.	Mitral regurgitation.	Both sides; probably more on right	.....	Slight in legs; disappeared before that in chest.	Probably slight ascites.		
10. J. E.	Aortic and mitral.	Possibly on right side; uncertain.	.....	Slight.	.....	.....	Fluid in chest suspected from high position of upper hepatic margin.
11. O. D.	Myocardial, mitral, and tricuspid dilatation.	Right.	.....	None.	Congest'd and fatty.	Left adherent, upper part; right adherent, upper part.	Hydrothorax recognized post-mortem.
12. J. T.	Aortic and mitral; suspected aneur'sm	Left.	.....	None.	.....	....	Uncertain signs of aneurysm.
13. G.V.C.	Mitral stenosis.	Right.	Aspirated four times	General.	Ascites; tapped once.		
14. M. C.	Mitral regurgitation.	Left.	.....	Slight; later considerable.	Congested; slight ascites.	Obliterative pleurisy of right pleural cavity.	Post-mortem.
15. P. K.	Aortic, mitral, and tricuspid.	Left.	.....	Considerable.	Enlarg'd.	Right pleura wholly obliterated.	Pericardial effusion.
16. S. T.	Mitral regurgitation.	Right; later left, but less marked.	.....	Marked.	Enlarg'd.		
17. A. L.	Mitral regurgitation.	Right, increasing considerably; left insignificant.	.....	Considerable.	Enlarg'd.		

DISCUSSION.

DR. OSLER: The history of these cases points to a local cause. It seems to me there are always three interesting points about them: First, the extraordinary chronicity, as they continue recurring, not for a few months usually, but for a few years; second, that the onset of the hydrothorax is usually very sudden; third, the almost invariable fact that these cases are mitral and the right side is chiefly involved. I have one patient now who has been under observation for over a year and one-half, and recall another who had recurrence for over two years.

DR. WILSON: There is another point that must be taken into consideration for a proper connection of all the factors in the causation of the disparity in the amount of fluid in hydrothorax of the two sides. In renal cases the hydrothorax is, in my experience, almost invariably a bilateral one. The exceptions are those in which an accumulation has been prevented on one side by the presence of old adhesions. Even in renal cases, however, the volume of hydrothorax is usually less on the left side than on the right. In cardiac cases the disparity is always in favor of a larger accumulation on the right side. The fact that such cases are usually instances of valvular disease or arterial sclerosis in which there is hypertrophy—in other words, cases in which the heart is larger than normal—is to be considered. If we regard the pleural cavities as closed spaces, the right being occupied by compressible lung tissue, the left largely by such tissue, but also to a large extent by an enlarged incompressible heart, we think of mechanical conditions, the enlarged heart on the left side offering obstacles to the transudation of fluid that the right side does not present.

DR. JANEWAY: I would like to speak of one case in which there was no proof of valvular trouble. It was a case seen years ago which was aspirated a number of times, where the character of the fluid drawn off gave it as a transudate, and yet caused much doubt in the minds of the experts who saw it as to the nature of the trouble. One thought it was a case of phthisis and advised the patient's going West. The second consultant, and a noted expert, said there was no heart trouble.

The first sound was valvular, but all I could say was that there was a weak heart and a right-sided hydrothorax. This condition continued for three or four months, and then finally (he had never had any evidence of renal disease) he became a little worse; there was dropsy of the limbs, with some albumin and casts in the water, and symptoms of nervous trouble. A neurologist was consulted, and said that the case was one of Bright's disease and had been from the beginning. The patient died eventually, and autopsy showed that it had been one of fibroid myocarditis, and there was a thrombus in the apex of the left ventricle.

DR. HARE: If I may amplify Dr. Wilson's view, it seems to me we ought to take into consideration the movements of the heart. It is perfectly possible that the diastole and systole may urge on the fluids on that side without influencing the other side.

I had recently a patient who developed this condition, and I was much impressed with the manner of onset. The patient, without any change in the cardiac symptoms, rapidly developed increasing dyspnea, and it was only after the most careful examination that commencing right-sided hydrothorax was discovered, tapped, and relieved. At the autopsy there was found mitral stenosis, and an aortic stenosis as well, which had not been discovered during life.

DR. JACOBI: In connection with this subject, and particularly with the case reported by Dr. Janeway, I would simply say that we all agree now that the subject of myocarditis has been too frequently neglected by practising physicians. A great many of the cases that come to us apparently with symptoms of valvular disease are really those of myocarditis. It is rather apt to have an edema in the early stage, in fact, as one of the first symptoms, while a valvular disease would not show any dropsy at all at an early period. This myocarditis need not be general, but often is only local, and it is quite possible that it may be overlooked, even after microscopic examination, because the specimen may happen to have been taken from the healthy part of the heart and not from the diseased portion.

DR. STENGEL: I would like to refer to one of my cases (Case I.) that bears out exactly the point which has been raised by Dr. Janeway.

CHRONIC MYOCARDITIS AND FATTY DEGENERATION OF THE HEART.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK.

CLINICALLY, these two expressions of cardiac degeneration are frequently most difficult to differentiate accurately. We have our suspicions based upon a fair interpretation of the case as a whole, and sometimes the results of the autopsy justify our probable diagnosis. Many times we believe we shall find not merely fibroid changes, or, indeed, simple fatty degeneration, but there will be a combination of both changes. In the advanced forms of fatty change particularly, and whenever we have in the history of the patient efficient causation of such alteration, our belief in its existence is very positive. There are, however, numerous instances in which our diagnosis during life is at best very problematical, and yet it seems to me any other diagnosis of what we observe falls short of seeming truth and is at best somewhat unsatisfactory to the practitioner. While we know, from example, in the graver forms of anemia, and notably in the so-called pernicious form, fatty degeneration of the heart muscle is no common finding, I do not believe that physicians are apt to consider that the heart may be structurally affected in the simpler forms.

It is true that many symptoms point to cardiac weakness. Notably we would put emphasis on lowness of the heart-sounds at times, on extreme rapidity of its beats, with sensations of fluttering and cardiac distress. Sometimes there is a systolic murmur which covers in part or wholly the normal sound. Frequently this is absent. Attacks of dizziness or faintness may come on readily and repeat themselves with little or no sufficient cause. I have seen such an attack where the patient was unconscious for a period of half an hour or more. During this period the pulse was very faint, some-

times almost imperceptible at the wrist. There was occasionally a lapse of pulsations at the wrist for one or two cardiac beats, accompanied with marked irregularity. The extremities were cold, the respiration shallow and suspirious. After such attacks, and when the patient's strength had partially returned, there was no enlargement of the heart which could be discovered, no abnormal pulsations either on the chest or in the neck, and no venous hum in the jugulars.

I am of the opinion to-day that such cases often mean beginning cardiac degeneration of the fatty type, and that any other interpretation inadequately expresses the best medical judgment. Of course, they require iron and arsenic to re-establish the blood condition. They are also temporarily benefited at times by the use of intestinal antiseptics; still, in order to bridge over the acute attacks we must give cardiac stimulants freely and repeatedly and aid with the heart tonics of strophanthus and strychnin judiciously administered. Oxygen also given systematically is of great help and must be insisted upon.

We all feel we know the usual gouty heart fairly well, viz., the heart affected with moderate hypertrophy of the left ventricle and adjoined to evidences of more or less fibroid changes in the kidney and general arteriocapillary circulation. Whenever this hypertrophy is no longer thoroughly compensatory and evidences of heart weakness develop, as shown by local and general signs and symptoms, we are frequently brought to the position of asking ourselves whether cardiac degeneration is present, and if so, its extent, variety, and nature.

Our diagnosis must be determined by several considerations independently, perhaps, of the underlying and evident gouty changes. It may be that the patient has been a free liver, is of corpulent frame, and has indulged more or less, and for a considerable time, in the use of alcoholic stimulants.

These conditions would tend to make us reasonably sure of the presence of some fatty degeneration of muscular fibre. The condition also of the liver, notably where it is torpid and enlarged and there is possibly some additional abdominal enlargement, with tension of the parietes, would make us suspect cirrhotic and fatty changes in this organ. The presence of ascites may remain doubtful

for weeks and months, and never, indeed, be accurately determined. Again, in a relatively short period succussion and palpation may unquestionably reveal abdominal effusion in small or moderate quantity. In these instances the pulse may never have increased tension, or only to such slight degree that our tactile sensations, or even the use of the sphygmograph, may not corroborate our suspicions, but simply leave us in reasonable doubt. Here, again, it is the skilful touch, the keen appreciation of local changes which proceeds from long, careful experience, or the expert and, may be, repeated use of the sphygmograph, which shall solve our difficulty. In any event, but particularly where our findings are positive, we believe that we shall detect an excess of fibroid tissue in the heart in certain spots between atrophied, compressed, or degenerated fibers.

The cerebral symptoms, which may be passing or more or less permanent, while pointing to cardiac degeneration, do not tell us positively whether the fibroid changes or fatty ones are predominant. If the mental activity of the patient has failed slowly and evidently for many months, if the memory be impaired, somnolence increasing, and even slight mental exertion be accompanied by great fatigue, slowness and difficulty of speech, and obvious lethargy, we are inclined to the opinion of marked fatty degeneration, always supposing the other signs and symptoms mentioned are present. If now the arterial tension remains high the coats are visibly thickened, knotty, tortuous, giving proof of decided atheromatous changes, we are prone to believe that the intracardiac condition will be more likely that of chronic myocarditis, with marked fibroid changes. Any calcification of the arteries, as of the radial or temporal, will only accentuate and confirm this judgement.

This condition we should not find except in very rare instances, unless the patient were one already of advanced years or the gouty dyscrasia were intense and of hereditary origin increased by bad habits of life, speaking mainly from the hygienic stand-point.

In some instances we are led to believe that on autopsy we should find the coronary arteries notably affected. These examples are especially those in which precordial pain and anxiety had been evident at times and with moderate or great intensity.

I have seen a patient, not long ago, a professional man, about fifty-five years old, who gave the following history: He had been a

careful liver so far as food and alcohol were concerned, but had for many years smoked immoderately and kept late and irregular hours. He had done much hard work in active professional life and in a literary way. He had been for many years a chronic dyspeptic, showing itself by slowness and impairment of digestion, belching of wind, and capricious appetite. He had never suffered from symptoms of heart weakness or distress. Calling to see him, I found him pacing the floor, with marked dyspnea, precordial distress, and great mental anxiety, and the feeling of impending disaster. The hands were cold and the face blanched; the pulse was regular and tolerably full; the radial arteries were thickened and there was apparently increased tension; the heart was enlarged, showing hypertrophous dilatation, moderate in amount. This attack had lasted twelve hours without relief spontaneously, and was increasing in intensity, as shown by the augmented distress. The swallowing of numerous soda-mint tablets, which frequently gave relief to simple dyspeptic conditions, was of no avail.

I prescribed immediately a heart tablet of strophanthus, digitalis, atropin, and nitroglycerin, and in a few hours there was great relief. The urine during the attack was high-colored and concentrated, but contained neither albumin nor sugar. In a few days he was about as usual. I advised repose from work and careful dietary, with the use of cardiac stimulation if required. In a short while he was better than he had been in many months and had had no recurrence of his anginose symptoms.

No doubt, to my mind, this patient has intracardiac changes, probably of the fibroid type. It is probable also that his coronary circulation is defective and that endarteritis is present. Did he have some temporary and incomplete obstruction of one or other of these arterial branches at the time of his attack? This I believe, although I cannot affirm it. I only know that no other diagnosis is sufficient to explain his symptoms satisfactorily. Probably the causes enumerated were all more or less contributory to the development of the attack. Judging by the sequence of events, I believe that nervous tone to the heart was partially restored by relative rest from work and that the stomachal condition was improved by appropriate dietary. The use of the cardiac tablets during the attack certainly gave marked relief and possibly prevented a fatal termination due

to complete clogging of one or both main arterial coronary branches

I have known of the case of another professional man, about fifty years of age, whose habits were not different from those of many tolerably successful ones at this period, residing in a large city. He worked moderately, but not unduly; he ate and drank with proper selection and due regard for his habits and peculiarities; he gave himself a fair amount of recreation, took long summer vacations, and was fond of the water and yachting. At times he had very slight attacks of dyspnea and precordial anxiety, which never meant absolute pain or great distress; indeed, these mild attacks occurred at infrequent intervals and disappeared spontaneously, and in a few minutes or hours at most. One afternoon, hastening home from his boat on the river to dine and meet his wife, who was anxiously awaiting him, as he was late, he had an attack of severe angina pectoris and died suddenly in the street.

The following description of the cardiac changes found at the autopsy is copied textually from notes kindly given me by the pathologist:

"Moderate degree of hypertrophy of left ventricle. Valves competent. Atheroma in mitral valve and in beginning of aorta. In latter situation this is most abundant about origin of coronary arteries, whose lumen is distinctly encroached upon by it. On opening of coronary arteries atheroma is found in their walls extensively beyond their origin. In this way their caliber is considerably narrowed. Microscopic examination of heart muscle reveals increase in pigment in cells about nuclei and a slightly granular condition of muscle-cells generally, but no distinct fat. There is no obscuration of transverse striæ and there is *no increase in fibrous tissue.*"[1]

Analogous instances to this are not infrequently met with. Of course, the precise nature, the degree or intensity of the signs and symptoms experienced during life vary greatly. In a similar manner the rapidity or suddenness of the fatal termination, if it occur, varies also very much. Whenever the coronary circulation is immediately and wholly obstructed, sudden death takes place,

[1] The findings at autopsy are here unusual, in that there was no occluding thrombus and the muscle changes were slight.

and one of several findings is evident at the autopsy. It may be that the coronary artery is filled up with an embolic plug, which has its origin in the heart either from a cardiac thrombus or from a detached portion of vegetation from a diseased valve or cusp of the mitral or aorta. In such cases the coronary arteries may be relatively free of disease, although frequently there may be even here a concomitant condition showing local degeneration, though slight in amount. Wherever—and this occurrence is much more usual—the coronary arteries themselves are more diseased, showing inflammation, thickening—endarteritis, in other words—or pronounced atheroma, with possible calcification at certain points, they are occluded with a thrombus.

The arteries may be occasionally affected and narrowed mainly or entirely at their orifices, or, what is truer ordinarily, the coronary arteries are thickened, tortuous, atheromatous, or calcified throughout the larger portion of their distribution. These changes have, of course, greatly decreased their lumen or the extent of their caliber internally, so that the heart has been imperfectly nourished by an insufficient blood-supply for a long period, and at a given moment a thrombus forms locally and almost inevitably, and a fatal result ensues, although, of course, in a somewhat less rapid manner than if an embolus has been the immediate and efficient cause of death.

The local changes of the heart muscle, in these latter cases particularly, partake of a fatty or fibroid character and are more or less localized or disseminated in their distribution, according to modifying general conditions. Moreover, the time during which the changes have taken place and the age of the patient have much to do with the character of these changes. As I have already pointed out, it is almost impossible prior to death and direct examination of the heart to state positively just what shall be found, so far as the precise changes or the limitations of the morbid involvement of the coronary arteries and heart muscle are concerned.

In old valvular troubles of the heart, whether they be of the nature of stenosis or regurgitation, in chronic pericarditis where the adhesions are tough and fibrous, in an advanced condition of hypertrophy of the heart, with probably much cardiac dilatation, fatty degeneration is almost surely going to occur at a given time, provided the patient's life is sufficiently prolonged; then, of course,

notable cardiac weakness, precordial distress and dyspnea, cyanosis, infiltration of the lower limbs, weak, unequal, and irregular pulse, deficient and concentrated urinary secretion, are some of the numerous painful phenomena with which we are all familiar.

In these cases we naturally expect and usually find post-mortem far more disseminated degenerative changes of the heart muscle than we do in the instances previously cited. As a rule, the left ventricle, and more particularly the portion of it near the septum, is specially affected. The columnæ carneæ—the papillary muscles—are frequently reduced in size, changed in color, soft to the touch, possibly giving a greasy feel, easily torn or lacerated, and showing to the naked eye indubitable evidences of fatty degeneration which microscopic investigation will merely serve to reaffirm. The right ventricle may also be degenerated in parts, although less frequently and it is now known that the auricles are sometimes in a certain degree degenerated, although this statement was formerly denied.

If there be chronic myocarditis present, which occasionally occurs, the heart muscle is hard and resistant in spots and very often diminished in thickness where this exists, owing to the deposit of fibrous tissue which has practically caused many muscular fibers to atrophy, degenerate, or almost or completely to disappear.

In those corpulent people who have accumulated flesh continuously, slowly, and in large amount, the heart is no exception to the great number of viscera which become more or less involved. The deposit of fat upon and around the heart usually seeks at first those regions where fat is deposited to some extent normally, and particularly in the grooves between the auricles and ventricles and along and over the intraventricular septum. Later, it is no uncommon finding to discover fat under the epicardium or the endocardium. Whenever this occurs the fatty infiltration has extended deeply into the heart muscle and between the muscular fibers to such an extent that the force of the heart-beats is notably lessened, and many of the phenomena which characterize true fatty degeneration of the cardiac muscle are present during life. No very long while passes under these circumstances, unless treatment is effective in checking the accumulation of fat in the tissues until the fat deposited penetrates the muscular fibers themselves and produces true fatty degeneration of the heart.

These obese persons are, therefore, always a source of special solicitude to us when we take care of them in any of their ills. All acute diseases in their instance are of moment, and what would be a relatively simple affair with a thin person or one with only moderate or healthful embonpoint is apt to take on a certain degree of gravity. A slight bronchitis, an attack of influenza, a mild rheumatic seizure, or a limited attack of acute pleurisy will almost invariably lessen their bodily strength very rapidly, and soon their respirations are much quickened, their pulse becomes rapid and weak, and their cardiac action so feeble as to require immediate and frequent stimulation. The only way to treat such patients safely is to suppress all bodily exertion as much as possible for a time and to lessen, if feasible, their mental care and anxieties. Even without any marked febrile movement they should be put to bed and kept there until the acute attack, whatever it be, has completely passed, during several days at least. Of course, if there be marked febrile reaction the urgency and necessity of this action on the part of the attending physician is even far more imperative; and here it is well to remark that in such cases, as frequently the rise of temperature is often only slight or moderate, the patient's immediate and nearest relatives are not at all alarmed and not infrequently consider the wise and careful, conscientious physician a great alarmist, when he is merely obeying his best judgment if he insists absolutely upon the importance of following out strictly his orders.

At first in some of these cases, and leaving out attacks of acute trouble for the while, the careful examination of the heart physically will not permit us to affirm that there is any notable cardiac enlargement; and even the heart-sounds, when the patient is in his usual health and free from physical exertion and not harassed with business or other cares, will not show any special weakness, irregularity, or notable murmurs; but often very slight exertion—as going up stairs, climbing a hill, hastening in even an ordinary walk on level ground—causes distress, and they will be in a panting condition almost immediately, become dizzy and faint, and the face is suffused with an undue pallor, or else their cheeks and eyes are congested and their lips are blue and cyanosed. These cases we all see—we meet them every day—and often, I am sorry to say, do not guide and direct them intelligently.

If the person affected with obesity is young I do not believe, as a rule, that the immediate outlook of the case from a cardiac standpoint has usually much gravity; and yet even then we must not ignore the possible outcome and the danger of dilatation of the heart resulting—more or less lasting and important—unless we insist upon proper dietary, exercises, and judicious medication. But in women, near the climacteric especially, and in men near or past middle life, we cannot be too formal about our protests to be careful and heed judicious medical counsels; otherwise we shall have soon to deplore an evident cardiac enlargement and dilatation, which from a prognostic stand-point are certainly very grave, as the underlying cause is often fatty degeneration of cardiac muscular fiber, and in view of the age and condition of the patient is very difficult, not to say impossible, to remove.

In young girls, particularly, obesity is apt to follow acute disease like scarlet fever or typhoid and to be allied with chlorosis. The anemia is sometimes corrected by proper treatment without too great lapse of time; again, it is most persistent and resists all our efforts for months and years. During this period such girls are liable to syncopal attacks and other symptoms which surely indicate pronounced cardiac weakness and cause much distress and anxiety to all concerned—patient, relatives, and physician. In older patients the blood may be of relatively good quality and not seemingly add to the distressing or merely uncomfortable symptoms.

In some women who have profuse menstruation; in those who are married and have had several children; in women at the time of the menopause—the amount of blood often lost at the monthly flow is excessive, and the result is that the bodily strength is greatly diminished and the blood examination shows great diminution in hemoglobin and the number and appearance of the red cells.

Here, again, I have no doubt that the anemia thus produced hastens considerably fatty degeneration of heart muscle and the subsequent development of cardiac dilatation. In these instances, if for some reason the patient is obliged to submit to an operation and take an anesthetic, of course the attending physician, surgeon, and, above all, the giver of ether or chloroform or even nitrous oxide, should be particularly careful. In uterine fibroids which require operation I would urge more than ordinary solicitude in administering anes-

thetics, and especially in corpulent women about middle age. These women are affected with several conditions which are apt to produce fatty degeneration of the heart. It may be that prior to the operation the heart had been thoroughly examined and was declared competent and probably free from more than a considerable degree of fatty *infiltration*, making part, as it were, of the increased fatty accumulation in the body not only in the cellular tissue under the skin, but also of several of the other viscera. During the course of the anesthesia, however, and subsequent also to the operation, general phenomena of cardiac weakness showed themselves, which, without doubt, at times hastened or, indeed, occasioned the fatal ending of the case.

Whether under these circumstances, as in one unfortunate case I have in mind, the cardiac failure would at all explain the rise of temperature and local evidences of peritonitis which developed, or whether these latter phenomena were merely due to some imperfection in the operative technique, or, indeed, to penetration and absorption of septic material in the abdominal cavity, I am not wholly convinced. What we do know is this, viz., when a sudden and great loss of blood occurs, accompanying the severe shock to the nervous system, and, indeed, the whole organism, inseparable often from the results of a very severe operation, we have conditions which may readily serve to explain increased temperature, paralysis of the bowels, local congestions of intense degree leading rapidly to inflammation, the formation possibly of purulent infiltration, and death.

Our overwrought theories of microbic infection, it appears to me, make us partially blind to the broad notions of general pathologic physiology, which I am confident will outlive narrow and confined notions of the origin and development of disease, and so it may be in the case referred to.

In no condition do we dread more the development of fatty degeneration of the heart than in that of chronic alcoholism. In all acute diseases, but particularly so in the pneumonia of adults, when we know we have to do with a chronic alcoholic, our prognosis of the outcome of the case should always be carefully guarded. No matter how mild the attack may apparently be in the beginning—no matter how hopeful we might be in other cases as to the future course of

the disease—in view, perhaps, of the small area of lung involvement and the mildness of the general reaction present, danger is always lurking and may show itself almost at any moment, either during the acute stage of the pneumonia or in the early convalescent period, by sudden pulmonary congestion or edema, with accompanying heart-failure; or, indeed, the heart itself may rapidly or suddenly cease to beat, and the patient die in a syncopal attack of dyspnea and apparent asphyxia, or a convulsive seizure resembling closely a so-called uremic attack. The slightest effort may bring on such a result. Going to stool, raising himself, or turning over in bed without the help of a nurse may be among several efficient causes which bring about instant dissolution Again, the fatal occurrence may come about without any accidental circumstance whatever to which we would direct attention.

Not only in acute diseases are these statements true, but they are almost equally true when the individual has apparently been in his usual health. Thus it is we hear of many cases of sudden death attributed to so-called heart-failure, which means nothing tangible or obvious, but which should mean fatty cardiac degeneration. If an autopsy is made it will frequently demonstrate the fact beyond reasonable doubt.

In certain autopsies carefully conducted, so far as visible appearances are concerned, a report is occasionally returned that no sufficient cause of death has been discovered. The heart is about of normal size, there is no valvular disease, and the cardiac fiber does not seem notably affected. There is assuredly no pallor of the heart muscle; the heart may not flatten out on the table and the muscle may not be easily torn or lacerated; indeed, the heart muscle is deeply stained or of more than ordinary deep red coloration. In some instances this staining is due simply to the inhibition of the muscular fibers with the coloring-matter of the blood due to changes in this fluid. While this appearance is oftener present in acute febrile disease than it is where no such intercurrent complication has taken place, yet the cardiac appearances may be as I have described them in chronic alcoholics who have died suddenly.

The microscopic examination of the cardiac fibers in these instances, if made—and it always should be made—will not infrequently reveal manifest granular or fatty degeneration of muscular

fibers, possibly limited, but more usually disseminated. Whenever the changes are limited we should be careful to examine the condition of the coronary circulation, and frequently there will be found endarteritis or atheromatous changes.

In the senile heart, especially among those persons who have led a moderately careful and regular life, we are more inclined to diagnose fibrous changes than fatty ones if the heart begins to show decided weakness, irregularity, and intermittences. With this condition there may be moderate enlargement—usually hypertrophous dilatation. There may be no abnormal cardiac murmurs, and frequently the pulse, instead of being irregular and weak, may be of good tension and very regular, showing trouble only by a little lack of fulness and undue slowness. Of course, the arterial coats both at the radials and temporals may be thickened, tortuous, and stand out prominently owing to the shallow layer of subcutaneous cellular tissue.

The urine in these cases may be in fairly good quantity, but is ordinarily of somewhat low specific gravity, without sugar or albumin. An occasional granular or hyaline cast is often discovered. With a tendency to constipation, which often exists, the quantity of urine eliminated in twenty-four hours will sometimes be decidedly below normal.

With any little fatigue, with any slight error of diet, with any prolonged exposure, with any excessive heat or cold, with any rapid change of temperature even, these old people are apt to feel poorly. They lose appetite, they sleep less well, their bronchial secretion is increased so as to produce annoying cough for some days, they are apt to become lethargic and inclined to doze frequently, and it is not uncommon to have them complain of feeling dizzy or faint. All these symptoms are unquestionably due in some instances at least to certain fibroid changes in the heart muscle. These changes are, however, not usually limited there; they are more or less disseminated everywhere in the arteriocapillary system, and several of the different viscera are notably affected, and particularly is this true of the kidneys, the liver, and the lungs. We have in these cases the best expression, without doubt, of the general disease so ably described originally by Gull and Sutton and so well added to by the labors of George Johnson and other able writers.

As regards the effect of syphilis in producing cardiac degeneration, either of the fibroid or fatty type, I have very little to say from the point of view of my own personal observation and experience. In a few rare instances, it is true, where the syphilitic poisoning was intense and the constitutional effects had become wide-spread by reason also of its duration I have seen the internal organs evidently much affected.

Syphilitic gummata of the liver I have occasionally observed, and in connection therewith there have been fatty and fibroid changes. Undoubtedly the same products may occur in the heart walls, although very infrequently in the ordinary routine of general hospital or private practice. Its possibility, however, should be kept in view, and wherever we have to do with those changes in deep-seated organs of syphilitic origin which clearly show its special virulence we should pay particular attention to the condition of the heart. If there are signs and symptoms pointing clearly to cardiac weakness coming on slowly and increasing constantly it is good clinical conduct to have our mind alive to the possibility of an intracardiac gumma and to the fatty and fibroid changes which may depend upon or result therefrom.

After what I have written, the prognosis and treatment of these structural changes should be considered. In general it may be said that if the process has come on with some rapidity, or if the cause be possible of removal, the prognosis is far less grave, at least prospectively, than if the contrary conditions are true. Of course, in the fatty change of the heart, which I believe possibly or probably exists to a certain degree, at least in a few anemic young women, this condition is undoubtedly curable in a shorter or longer time by judicious methods of treatment. If the anemic state should, on the contrary, become of a more advanced or pernicious type, we all know that while we may and do obtain temporary good effects, which for a while at least may seem to promise a permanent cure, our hopes are apt to be in vain. This is thus far the history of the medicinal effects of large and increasing doses of arsenic and the use of intestinal antiseptics according to the method of Hunter in the treatment of pernicious anemia. The able and exhaustive report of Cabot before the Association of American Physicians, May, 1900, would serve only to confirm the correctness and sadness of this view.

In all instances, of course, where the anemic condition and the accompanying cardiac degeneration, probably fatty, depends upon or is occasioned by malignant, incurable disease, so recognized at the present time, we cannot properly hope for any amelioration of the cardiac changes. In most instances where the alcoholic habit has been largely instrumental in bringing on signs and symptoms of cardiac fatty degeneration and similar changes in other viscera—if these changes are not too far advanced and if the alcoholic habit be entirely suppressed—we may reasonably hope in many examples for a measurable degree of improvement in the physical condition of the patient and possibly for a complete cure. This happy result can only be obtained with considerable time, however, and by absolute attention to abstemious habits of life and, above all, by complete abstention from alcohol in future. Of course, if the alcoholic habit has been an excessive one and long continued, and if the patient has already reached middle life or passed beyond it, the ultimate outlook of the case is far less hopeful. In this matter, however, personal idiosyncrasy and constitutional tendencies should always be considered and much weight given to their due estimate.

I have known certain individuals to have a pronounced alcoholic habit of many years' duration, and yet during a large portion of the time they have shown no morbid symptoms or signs of special moment resulting therefrom. When morbid phenomena develop finally in these cases, pointing unerringly to involvement and degeneration of the heart muscle, I still feel a reasonable hope that they may be able to arrest their disease, provided always that I can persuade them to restrain absolutely their alcoholic appetite.

In other cases so soon as the cardiac degeneration is clearly present the onward march of the disease takes place apparently without halt or hinderance. The march onward and downward may be slow or rapid, but, unfortunately, it is sure, and our best remedial means are ineffective to delay or arrest its course.

In certain obese persons, by a proper system of diet and exercise and suitable cardiac tonics at times combined with the continuous and judicious inhalation of oxygen during weeks and months, we may sometimes obtain very good effects. The prolonged use of potassium iodide in these cases, given in moderate doses, always supposing it is well borne by the stomach and eliminative organs

(skin, lungs, and kidneys), is in the judgment of many capable observers very useful and takes the place oftentimes of nitroglycerin and the nitrates with great advantage.

A few observations of individuals, young or past middle life, have made me believe that the treatment of Nauheim in well-selected cases, and managed with discretion and good judgment and with a mental eye single and devoted to the best good of the patient, has been unquestionably of great use for a time. The great risk of this spa treatment, as of all others, resides in the fact that even intelligent, cultivated physicians, here as elsewhere, become in a sense the victims of their own exaggerated enthusiasm, and when a patient comes under their care they are apt to push their treatment inconsiderately perhaps and sometimes too far.

Or it may occur—I have known such a case—that an individual past the meridian of life has been sent to Nauheim for treatment by his family physician, and although the patient when he reaches the springs is in no condition to go through the spa treatment—or originally, even, may not have been a suitable case for these procedures, yet, either owing to his preconceived notions or to the stress he lays upon carrying out what he was ordered from home to do, the local practitioner of Nauheim permits the following up of what perhaps, if his better judgment had acted coolly and deliberately, he would not have permitted, or in another case have only permitted in a very limited measure.

In some cases one course of treatment at Nauheim may be decidedly useful, but unfortunately is not completely successful in establishing a cure. Such a patient is sometimes told to return another season, or another, and better results may or will be obtained. This, unhappily, is an error fruitful of bad consequences. The patient has really obtained all the good possible from the saline carbonic acid baths and the regulated resistance movements. It would have been far better for these persons, in my judgment, if they had remained away from the spa later and if they had sought from other means all the improvement they could fairly hope for.

It is the wise, conscientious physician, who is thoroughly familiar with the personality, habits, and surroundings when at home of these patients, who should really guide and direct them. I say it most regretfully that oftentimes his voice is like as one "crying in the

wilderness," and the wisdom of his forethought, wide knowledge, and clear-sightedness is rarely or perhaps never fully recognized. In senile changes of degenerative type affecting the heart, and especially where interstitial fibroid changes occur, accompanied usually, as I have already said, by more or less general changes throughout the whole arterial system, a wise conservatism should always prevail. It is utter foolishness to suppose that we can modify in any appreciable degree what has very slowly and surely taken place, and what is, after all, many times only the outward and visible expression of the progress at times or the result of "anno domini," from which man no more than other animals is exempt.

There is a natural growth and natural decay, and these fibroid changes in the heart and vascular circulation are to be wisely regarded as nature's showing in due season. In such cases, therefore, treat symptoms as they arise with the hope of temporary relief and temporary benefit many times, but no more hope to arrest or change the inevitable permanently than to change the river permanently in its course by an insignificant and temporary dam.

In the fatty degeneration which complicates chronic valvular cardiac conditions and is either the cause or the result of cardiac hypertrophy or dilatation something may still be done.

The general nutrition of these patients may be kept up by suitable food, and their emunctories may be properly stimulated when required by baths, diuretics, and gentle laxatives. Breathing pure air and gentle exercise in walking will sometimes prove remedial. The blood should be kept in good condition, and tonics may be required. Heart stimulants are often temporarily useful. In the event of evidence that the condition is not progressing favorably, strychnin is advantageous when continued for some time, with occasional interruptions, in moderate doses. Where there is much arterial tension, with marked dyspnea, potassium iodide, if well borne, will give temporary relief and occasionally prove permanently beneficial. All sudden or great efforts should be most carefully avoided, and especially is this true in the secondary great hypertrophy which follows aortic regurgitation, whenever the heart shows that its walls have become hopelessly degenerated. In these instances it is that many sudden deaths occur, as the records of our hospitals show, as well as occasionally experience in private practice.

In cases of suspected syphilitic degeneration affecting the cardiac muscle, potassium iodide, freely given, or the mixed treatment wisely ordered according to circumstances should be our main reliance.

In writing the foregoing paper I might have insisted more than I have done upon the purely pathologic aspects of my subject; I might, indeed, have given a careful description of pathologic findings in these cases at the autopsy when it was made, and especially when made with particular reference to the condition of the cardiac walls and the coronary circulation. To have done so would have lengthened my paper unduly, and would, moreover, have taken away perhaps part of the interest attaching to it as a clinical study, upon which I would place special emphasis.

Having said this by way of an explanation I would now crave attention for a few words from the point of view of the gross and minute lesions present in cardiac muscles in different instances. Wherever the heart is notably affected with fibroid changes the muscle there becomes tougher and more resistant, beside showing thinning of heart walls in places. In the spots thus affected there is a yellow-whitish coloration, which indicates somewhat the probable nature of the degeneration. This degeneration is prone to occur in patches and especially in certain regions of the left ventricle and near the septum and apex than elsewhere. Under the microscope the parts affected are shown often to be almost wholly composed of fibrous tissue.

In other cases, while the fibrous tissue is in great excess between the muscular fibers, the latter still are present but atrophied or degenerated more or less. The nucleus has sometimes disappeared as well as the striæ, and there may be more or less pigmentary deposit in the form of granules, regularly or irregularly distributed. Wherever the nucleus of the muscle still exists the pigmentary granules are apt to be present in larger numbers about it than elsewhere.

The primary fibers are occasionally almost homogeneous in appearance. Alongside of fibers much atrophied or degenerated there may be others relatively healthy.

In chronic fatty degeneration of the heart muscle, especially if it is at all advanced as to its stage, the color of the muscle is notably pale and yellow in places. Sometimes, however, where the changes

are not so far advanced, at least in spots, but more generally disseminated, the heart muscle, particularly of the ventricles where the degeneration is most pronounced, is less changed in color from the normal. However, in these instances the muscle has lost its consistence, is very flabby, and the heart flattens out and loses somewhat its healthy outline on the table; beside it has lost resistance and is easily torn and lacerated. Under the microscope the diseased fibers may show very numerous granules, or at an ulterior stage these granules may be replaced by many glistening, shiny, very refringent round bodies of large caliber, which evidently are oily or fatty. Here, again, the nucleus of the muscle may or may not have become degenerated or have disappeared entirely. The same is true of the lateral striæ and the longitudinal fibrillations.

There may sometimes be an overgrowth of pigment granules. These granules may be deposited in the muscular fiber itself or in the interstitial connective tissue between the fibers. The pigmentary granules may be more or less irregularly placed. Usually there are a larger number near the muscle nucleus. Occasionally the whole fiber may be larger than normal and appear almost entirely homogeneous.

Alongside of some fibers completely degenerated there are others which are relatively healthy or diseased only in parts. The connective tissue between the fibers in typical fatty degeneration of the muscle is usually not much, if at all, increased in quantity. In other cases, especially where there are fibroid changes throughout the vascular system and in different viscera, there may be a considerable increase of interstitial connective tissue and also pronounced fatty degeneration.

For further and more complete and accurate knowledge of the pathology of these cases I would direct my hearers to the best modern treatises on cardiac disorders, among which that of Gibson seems to me particularly valuable. To this author I feel especially indebted for much valuable knowledge, which I have not hesitated to utilize, and to whom I now give full credit.

ON THE CLASSIFICATION OF INTOXICATIONS FROM A PATHOLOGIC STAND-POINT.

By J. GEORGE ADAMI, M.D.,
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All actual chemical substances which have a deleterious action upon the cells of the body we speak of as poisons. We may thus accept the definition of Kobert that "poisons are non-organized substances, organic or inorganic, existing within the organisms or introduced there from without, which from their chemical constituents are able under certain conditions to be harmful to living beings by destroying or affecting their health or relative well-being."

Intoxication we must regard as the series of changes occurring in the organism in consequence of the action of such poisons.

A study of the substances which are able to enter into chemical combination with the cell substance shows that intoxicants or poisons are only such relatively; substances are harmful only when present in sufficient quantity either to set up molecular disturbance in the protoplasm of the cells or to arrest normal molecular changes in that protoplasm. Conversely, all substances capable of solution in the body fluids and absorption into the cells composing the body are also capable of acting as poisons, because their effect upon the cells depends on the extent of their absorption, and above a certain point, the limit varying with each substance, their action is unfavorable to the continuance of orderly cell processes; so that, to mention the extreme example, water introduced into the organism above a certain amount (*e. g.*, 60 c.cm. per kilo of body-weight) is found to be a poison, for it both causes the fusion of hemoglobin out of the red corpuscles and so prevents due oxygenation, and, being absorbed by the cells of sundry tissues in excessive amounts, it deleteriously affects the due activity of those cells.

It follows, therefore, that the number of potential poisons is enormous, and it can easily be understood that the effects of these poisons, the intoxications, are most varied. How are we to classify these intoxications?

There is no special group of reactions in the organism following upon the action of animal, vegetable, and mineral poisons, respectively, nor can we gain any broad conception of the mode of action of special sets of poisons by this classification; the actions of certain poisons belonging to one group are simulated by the action of poisons belonging to the other. Thus, for pathologic purposes, the old, familiar classification into animal, vegetable, mineral, and gaseous is absolutely futile. Nor, again, can we as yet make a classification acording to the chemical composition of the poisons, for in attempting this we meet with several difficulties. We have to recognize that a given substance has more than one action, that studying individual organs and tissues one form of poison differs often in its results from another which chemically may appear to be closely allied, and, thirdly, that the same poison acts differently upon the various tissues according to the degree of its concentration. We are, in short, compelled very largely to classify the changes recognized within the tissues, and from these changes to classify our intoxications.

Proceeding along these lines we can by analogy determine the essential nature of processes little understood. When, for example, to quote the researches of Bardeen and those of Dr. J. McCrae, which I am bringing before this Association, we find that the changes occurring in the lymph glands and kidneys in diphtheria are curiously simulated by the changes in these same organs which follow upon superficial burns, we recognize that in the systemic results of severe burns it is not the shock and nervous disturbance which are the only factors at work, but that at least an important factor is evidently a toxemia, or the entrance of some poison into the general systemic circulation, corresponding in many details with the toxins or bacterial poisons.

There is, however, another mode of classification which is distinctly valuable, and to which I would to-day especially call attention; because, while its value is recognized, the various terms elaborated in connection with this classification are employed so vaguely and so wrongly that either those terms must be completely tabooed, or,

on the other hand, an attempt must be made to employ them with a clear understanding of what they mean.

The first of these alternatives is, I think, impossible. When a term becomes widely employed it is an indication that it is definitely useful, and no amount of academic discussion will lead to its discontinuance. All that we can do is to see that it is employed correctly. It is to von Jaksch, I believe, that we owe the introduction of the terms *exogenous* intoxications and *endogenous* intoxications; the exogenous being set up by poisons introduced from without, the endogenous by poisons developed within the system.

A little consideration will show that we have to proceed with great caution in the employment of these two terms. In the first place we have to recognize that a poison introduced into the system from without, while most liable to produce an exogenous intoxication, may also set up one that is endogenous, and, conversely, that a poison developed within the body—one that is endogenous or intrinsic—may induce similarly either an endogenous or an exogenous intoxication.

Let me here explain more fully. With regard to the extrinsic poison, this may produce its effects in two ways—either by acting directly upon the cells of the organism, and by that action causing immediate disturbance, in which case it sets up an exogenous intoxication, or, indirectly, in its action upon the cells of certain organs it may lead to perverted activity of those cells, to modified internal secretion on the part of the same, and it may be these products of perverted cell activity, rather than the introduced poison, which set up the main disturbances, developing a condition of endogenous intoxication. Similarly, while the products of cell activity under certain conditions are liable to cause direct disturbance in the various tissues, so setting up an endogenous intoxication, it has also to be recognized that occasionally these substances only act after they have been discharged into the ducts and passages of the body, where, accumulating, they may be reabsorbed; in which case we really have to deal with exogenous intoxication, for it is necessary to lay down that any intoxication due to substances absorbed from outside the system are to be regarded as exogenous, whether the poison be manufactured previously within the system or not. Indeed, if we are to employ these terms aright it is necessary to keep clearly and

constantly in mind the distinction between *the poison* and *the intoxication*. This is especially necessary in connection with the endogenous intoxications. Here, in the first place, we have to obtain a very precise understanding of what is meant by the term endogenous, for some would speak of poisons produced by the organism itself as being the only endogenous poisons. This, I think, is wrong. The strict meaning of the term demands that all intoxications due to poisons *generated within* and acting within the system should be regarded as endogenous. Thus we have to recognize two broad groups of these intoxications, namely, endogenous intoxications of the first order, due to the action of substances developed by the body, or autointoxications, and parasitic intoxications, or conditions due to the toxins of bacteria or the discharges of larger parasites, generated within the system.

It is more especially in connection with the autointoxications that confusion has arisen, and this confusion is worse confounded by the failure to recognize what is within and what without the system. According to vulgar parlance, the contents of the alimentary canal are a part, and an important part, of the "inside" of the individual, yet, strictly speaking, the food taken is not truly within the system until it has been absorbed by the cells of the organism. Diagrammatically, we can represent a median sagittal section of the body as follows:

It is seen that only that which is in the shaded portion is really within the body; hence intoxication arising from the absorption of substances from any point outside of the shaded area must be regarded as exogenous. Now Bouchard, who popularized if he did not originate the term autointoxication, and following him the French pathologists in general—and not only French pathologists, but other writers in other countries—have started from this popular notion that the contents of the alimentary canal are within the body, and most unfortunately have classed all the toxic results not only of perversion of cellular and tissue activity but also of gastrointestinal fermentation and the absorption of products of bacterial activity in the intestinal contents under the one indiscriminate heading of autointoxication. Indeed, they regard these last as the most important of the autointoxications, and starting thus with a vague and indefinite idea of what constitutes autointoxication they make no sharp distinction between the two forms of endogenous poisons, namely, microbic and somatic or cellular. Everything is blurred, and as a consequence this term autointoxication, not being sharply defined—a term which is capable of being of the greatest utility—has fallen into disrepute simply because of this want of proper definition.

We see discussions, for example, on gastrointestinal autointoxication. What do the writers mean when they employ the term? Any one of the following conditions might be intended when it is employed in this way, namely:

1. That the secretions of the alimentary canal discharged into the intestines and there modified are reabsorbed, or, in other words, that we are dealing with an intrinsic somatic poison which sets up an exogenous intoxication.

2. That the intoxication has been caused by the multiplication of intestinal bacteria and the absorption of their products of growth, or that we are dealing with an extrinsic poison causing also an exogenous intoxication.

3. That the intoxication is caused by the interaction between the bacteria and the foodstuffs and contents of the alimentary canal; here again we are dealing with a purely exogenous intoxication.

4. That it is due to an interaction between the intestinal bacteria and the secretions, or that it is exogenous, but developed by a mixture of intrinsic and extrinsic poisons; or, lastly:

5. That the toxins absorbed from the intestine, whether of bacterial origin or derived from the breaking down of foodstuffs, when absorbed lead to a faulty metabolism, and that as a result of the consequent perverted activity of the cells of sundry organs those cells discharge into the blood poisonous products, and so we have to deal with an endogenous intoxication induced by extrinsic poisons.

From a study of these possible meanings of the term it is seen that, so employed, clearer conceptions are quite impossible. Apparently those who use the term gastrointestinal autointoxication refer in general to the effects of bacterial action upon foodstuffs. If they mean this, then the condition is as much an exogenous intoxication as is the result of drinking carbolic acid.

As I have already stated, it appears to me impossible to banish the term autointoxication entirely. What is necessary is that we must define clearly the conditions under which it may be used. So I would urge that *an autointoxication is an intoxication set up by the action of substances formed by or from the cells of the body; that is to say, either by the secretions of those cells or by the products of their disintegration.* Such autointoxication is endogenous when the poison so formed acts without any preliminary passage out of the system; is exogenous when it is due to reabsorption of the secretions, as, for example, when the obstruction of a duct is followed by reabsorption of the excretion. Such exogenous or indirect autointoxications are rare and of slight importance.

We thus arrive at the following classification of the intoxications in general:

I. EXOGENOUS: due to the action of poisons entering the system from without.
   1. *Exotic,* or introduced: due to the action of substances foreign to the organism which gain entrance through the skin, the digestive, the respiratory, or the genitourinary tract.
   2. *Indigenous,* or excretory.
      (*a*) Indirect autointoxication: due to the absorption of retained excreta.
      (*b*) Disintegrative: due to the absorption of decomposition and fermentation products developed in the external secretions through the action of those secretions.

II. ENDOGENOUS:

1. *Direct autointoxications.*
   (*a*) Internal secretory: due to the action of excessive or unneutralized or modified discharges from the cells of one or other tissues acting directly upon the other tissues of the body without previous discharge from the system.
   (*b*) Disintegrative: due to the action of the products of decomposition and necrosis of one or other tissues acting in a similar manner.
2. *Parasitic.*
   (*a*) Microparasitic, the infections.
   (*b*) Macroparasitic.

I suggest this table for your consideration, believing that if the terminology here suggested be adhered to we shall arrive at greater precision and clearer thought in the matter of the intoxications.

EXPERIMENTAL YELLOW FEVER.

By WALTER REED, M.D.,
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CONTRACT SURGEONS, U. S. A.

SUBSEQUENT to the presentation of our paper to the Pan-American Congress[1] in Havana, we succeeded in producing some additional cases of yellow fever at our Experimental Sanitary Station near Quemados, Cuba. We have thought that brief reports of these cases, to be followed by remarks on experimental yellow fever from the clinical point of view, would be of interest to the members of this Association, and especially to those who reside in sections of the country where each year yellow fever is liable to appear in epidemic form.

Perhaps it might be well to recall the fact that the cases of yellow fever here to be recorded were produced like those heretofore reported by us, under strict quarantine regulations and at a special experimental sanitary station.

In the series of twelve experimental cases produced at this camp during the period from December 5, 1900, to February 7, 1901—an interval of sixty-five days—it should be borne in mind that the order of occurrence exactly corresponded with the order of inoculation, except that Case II.—inoculated at 4 P.M., December 8, 1900—having a longer period of incubation than Case III.—inoculated at 10.30 A.M., December 9, 1900—the order of their relative occurrence became reversed.[2] Moreover, the attack always followed

[1] The Etiology of Yellow Fever. An Additional Note. Read at the Pan-American Congress, Havana, February 4-7, 1901.

[2] These cases were reported in our Additional Note.

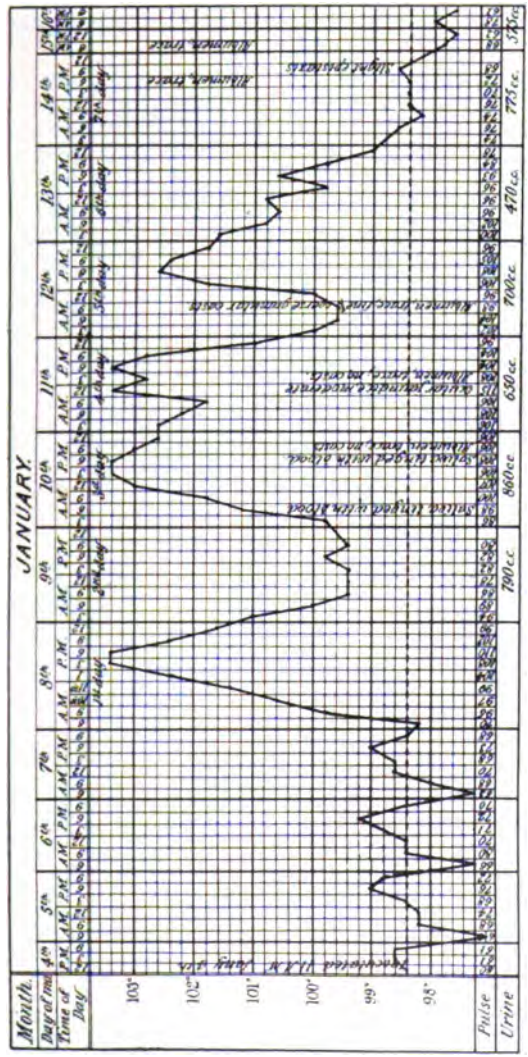
within the period of incubation of the disease, and concerned only those non-immune individuals who had consented to submit themselves for experimentation. Of a total of sixteen individuals who thus consented, fourteen contracted yellow fever; whereas of five non-immunes, who did not consent and were therefore not subjected to experimentation, none acquired the disease, although otherwise placed under exactly similar surroundings. In its occurrence, therefore, at this station yellow fever strictly obeyed the behests of the experimenters, both as to place and time of occurrence. Recovery took place in all cases.

(A) *Cases Produced by the Injection of Blood.*

CASE I.—W. J., American, non-immune, aged twenty-seven years, in quarantine since December 20, 1900, with his full consent at 11 A.M., January 4, 1901, was injected subcutaneously with 2 c.c. of blood taken from the general circulation of a case of mild yellow fever at the beginning of the second day of the disease, and having a temperature of 100.8° F. The subject, who had been in strict quarantine at this station for the period of forty-five days, remained in his usual health until the early morning of January 8th, when he complained of slight frontal headache. At 6 A.M. his temperature was 98.2° F. and pulse 70. At 9 A.M., temperature 99.8° F., pulse 95; frontal headache increased, with slight chilly sensations in the feet and lower extremities. There was some congestion of the eyes, and his usual florid complexion was heightened in color. At 10.15 A.M., temperature 100.6° F., pulse 97; complains of some pains in the lumbar region. At 11.20 A.M., temperature 101.4° F., pulse 99. The height of the febrile paroxysm was reached at 3 P.M. the same day, when the temperature was 103.4° F. and pulse 108. The facial expression was now characteristic of yellow fever. The eyes were deeply injected and watery, and the face much suffused. Photophobia moderate; frontal headache and backache severe. The skin was moist. The remission occurred at the end of twenty-four hours—9 A.M., January 9th—when the temperature had fallen to 99.4° F. and the pulse to 86. The subsequent history was that of a case of yellow fever of moderate severity. Albumin was found in the urine at the end of the sixty-first hour. There was some bleeding from the gums on the third day, and moderate ocular jaundice on the fourth day. Fever disappeared on the morning of the seventh day. (Chart I.)

CASE II.—W. O., American, non-immune, aged twenty-eight years, in quarantine since December 20, 1900. On January 8, 1901, at 9 P.M., with his full consent, he was given by subcutaneous injection 1.5 c.c. of blood taken from the median-cephalic vein of Case I. just twelve hours after the beginning of the attack and when the temperature was 102.4° F.—that is, just after the first febrile paroxysm had begun to decline. The subject remained in his usual condition during the following two days.

January 11, 1901, at 6 A.M., his temperature was 98.8° F. and pulse 70. He complained of being disturbed by dreams during the night and had some frontal headache. At 9 A.M., temperature 100° F., pulse 77. At 10.15 A.M.,


JANUARY.
Month.
Days of the Month
Time of Day
Pulse
Urine
103°
102°
101°
100°
99°
98°
Sulphate Magnesia 4 drachms
Sulphate Magnesia 4 drachms
Sulphate Magnesia 4 drachms

reached. Headache and backache were now much complained of. The facial expression was characteristic. The remission occurred at the end of twenty-four hours, lasted one day, and was followed by a very moderate secondary fever. A distinct trace of albumin was found in the urine passed at 2 A.M. January 12th, seventeen hours after the attack began. A few

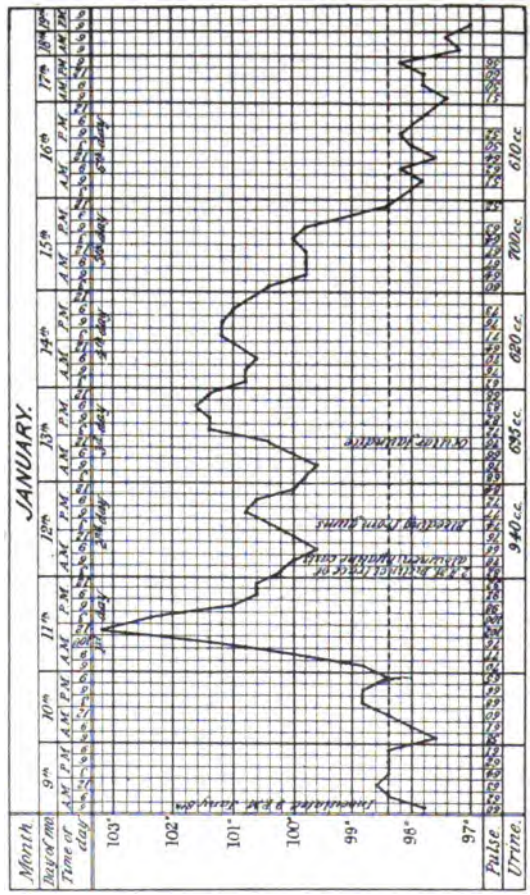


CHART II.—Yellow fever produced by injection of 1.5 c.c. of blood. Period of incubation, 2 days 12 hours.

hyaline casts were also present. Slight bleeding from the gums occurred on the second and third days of sickness. The character of the attack in this case was very mild. The albumin, which at no time amounted to more than a distinct trace, did not disappear, however, until January 24th. (Chart II.)

CASE III.—W. F., American, non-immune, aged twenty-three years, was,

with his full consent, at 1 P.M., January 22, 1901, injected subcutaneously with 0.5 c.c. of blood taken on the second day from the general circulation of a severe case of yellow fever, which was fatal on the seventh day of the disease. The patient's temperature when the blood was withdrawn, was 103° F. and pulse 90. The subject remained well during the following day.

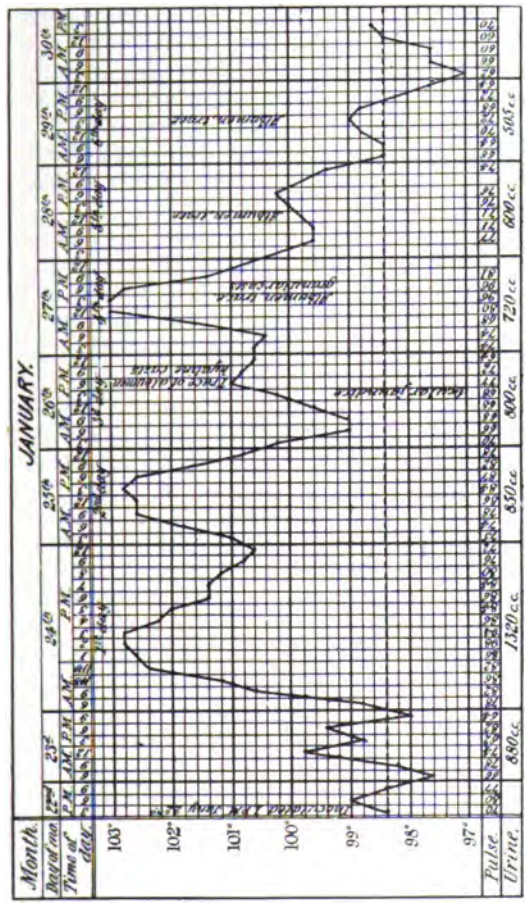


CHART III.—Yellow fever produced by injections of 0.5 c.c. of blood. Period of incubation, 3 days 1 hour.

January 24th, at 6 A.M., his temperature was 98.4° F., and pulse 78. He partook of a hearty breakfast at 6.30 A.M., which he vomited soon afterward. At 7 A.M. he complained of dizziness and general lassitude. Temperature 98.4° F., pulse 78. At 9 A.M. chilliness complained of, but there is no record of temperature or pulse. At 9.30 A.M., temperature 100.6° F., pulse 82; frontal headache well marked. Eyes already injected and face

slightly suffused. At 10.30 A.M., temperature 101.2° F., pulse 86. An hour later his temperature was 102.6° F. and pulse 82. The height of the primary paroxysm was reached at 1 P.M., when the temperature was 102.8° F. and pulse 98. At this hour photophobia was well marked and constant complaint made of severe frontal headache and backache, together with pains in the lower extremities. The skin was moist. The remission occurred at the end of thirty-six hours. The subsequent course was that of a case of yellow fever of moderate severity. With the return of the secondary fever there were present sharp backache and headache. Albumin appeared in the urine at the end of fifty-seven and a half hours. Ocular jaundice was present on the third day and thereafter until convalescence. The gums did not bleed, although they were swollen and injected. Fever subsided on the sixth day, and albumin disappeared on the eighth day. (Chart III.)

CASE IV.—J. H. A., American, non-immune, aged twenty-two years, with his full consent received subcutaneously at 12.15 P.M., January 25, 1901, 1 c.c. of blood taken from the median cephalic vein of Case III. just twenty-seven and a quarter hours after the commencement of the latter's attack of yellow fever (temperature 100.6° F.). The subject remained in his usual condition during January 26th and 27th, except that on the afternoon of the last-mentioned date he complained of occipital headache. This was present on the following morning, January 28th; otherwise he felt well. His temperature at noon was 98.6° F., and pulse 68. Occipital headache continued. He partook of a dinner with fair appetite. He was not seen again until 3 P.M. In the meanwhile, at 1.15 P.M., the subject states that while sitting alone in his tent he began to feel cold, and that this was quickly followed by a decided chill with increase of headache. He noted the hour in writing at the time. At 3 P.M. his temperature was 103.6° F. and pulse 120. The eyes were intensely congested and the face deeply suffused. The patient was very restless and complained bitterly of occipital headache and backache. Photophobia was very marked. He vomited several times within the next two hours; skin hot and dry. The height of the primary paroxysm was reached at 3.30 P.M., at which hour the temperature was 104.2° F. and pulse 120. The subsequent history was one of severe yellow fever. There was no remission in the fever until the fourth day, when the temperature fell to 101.2° F. Now, for the first time the patient ceased to complain of occipital headache and backache. Albumin appeared at the end of eighteen and a quarter hours (7.30 A.M., January 29th). A few hyaline casts were also present at this time. The specimen of urine passed at 6.40 A.M. January 30th contained albumin one-twentieth by volume and many fine and coarse granular bile-tinted casts. Ocular jaundice appeared on the third day. The skin of the face and of the anterior part of the neck and thorax was tinted on the fourth day. This rapidly became intensified and general. The secondary fever lasted about thirty hours, the temperature falling to 97.2° F. at 12 o'clock midnight of the fifth day. Marked

fluctuations of temperature continued until the eleventh day of illness. Recovery was slow and much delayed by the development of a carbuncle in the left sacral region. A trace of albumin was still present on March 1st, thirty-two days after the attack had begun. (Chart IV.)

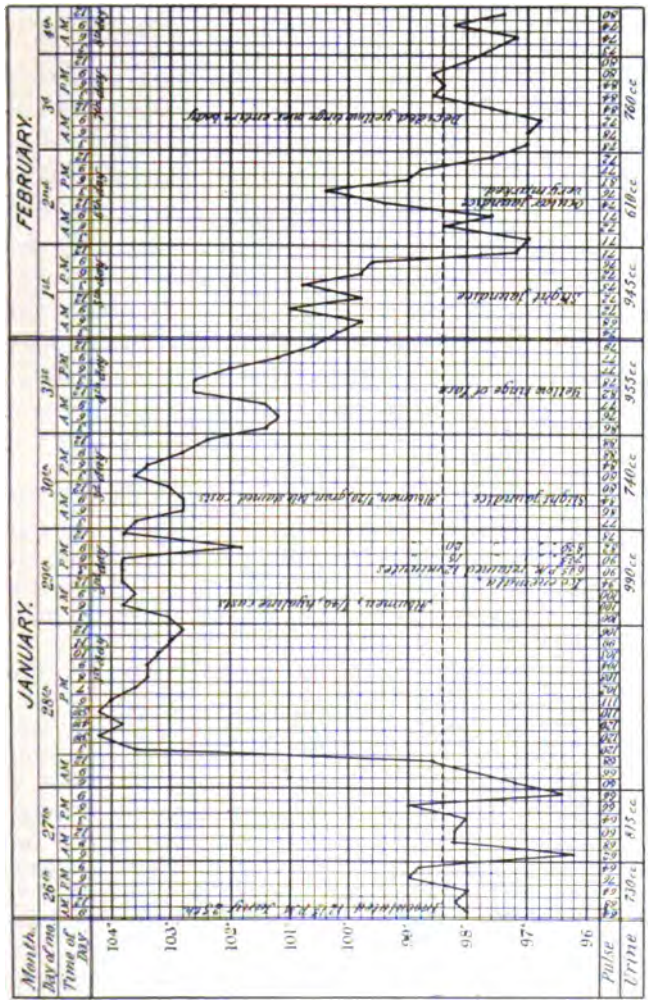


CHART IV.—Yellow fever produced by injection of 1 c.c. of blood. Period of incubation, 1 day 19 hours.

The production of yellow fever by the injection of blood taken from the general circulation is of much interest as showing, first, that the parasite is present in the blood at least during the early

stages of the disease; and secondly, that its passage through an intermediate host, although this would seem to be nature's method, is not essential in the life-cycle of this parasite. Thus, yellow fever is analogous to the malarial fevers in that it may be produced either by the bite of a certain species of mosquitoes or by the injection of blood taken directly from the general circulation.

Another point to which we have elsewhere referred, but which we consider of sufficient importance to here bear repetition, is that in each of the foregoing cases of experimental yellow fever produced by the injection of blood, careful cultures made from the same blood drawn from the vein immediately after injection, or, as in one instance, made from the same syringeful of blood that conveyed the disease, failed to show the presence of Sanarelli's bacillus. In one case colonies of staphylococcus pyogenes citreus were obtained, while in the remaining three cases no growth whatever occurred. The exclusion of the bacillus icteroides from further consideration as the specific agent of yellow fever would, therefore, seem to have been conclusively determined by these experiments.

(B) *Cases Produced by the Bite of the Mosquito. Culex Fasciatus.*

CASE V.—L. F., American, non-immune, aged twenty-eight years, in quarantine since December 20, 1900, was with his full consent at 3.30 P.M., January 19, 1901, bitten by three mosquitoes that had been contaminated, thirty-nine days previously, by feeding on the blood of a well-marked case of yellow fever on the third day of the disease.

The subject remained in his usual condition of health until the afternoon of January 23d. At noon of this date his temperature was 97.8° F. and pulse 72. Soon after this hour he took to his bed, complaining of frontal headache and general lassitude. At 3 P.M. his temperature was 99.2° F. and pulse 78. At 4.10 P.M. the temperature was 100° F. and pulse 104. A sense of chilliness, especially of the lower extremities, and increased frontal headache were now complained of. Eyes already injected and face flushed. At 5 P.M. the temperature was 101.2° F. and the pulse 104. The height of the paroxysm was reached at 8.20 P.M., at which hour the temperature was 103.6° F. and pulse 110. The eyes were deeply congested and photophobia very marked. Headache and backache were so intense as to cause the patient to complain bitterly. He vomited once at 9 P.M. January 24th, 3 A.M., the temperature had fallen to 100.2° F. and the pulse to 104, but with only slight amelioration to the patient's discomforts. At noon the thermometer marked 102° F. Remission occurred at the end of thirty-three hours, with marked diminution of all disagreeable symptoms. The secondary fever, attended by increased headache and backache, lasted four days, the temperature dropping to nor-

mal at 6 A.M. of the seventh day. The case was one of moderate severity. Albumin appeared in the urine at the end of the forty-second hour. Ocular

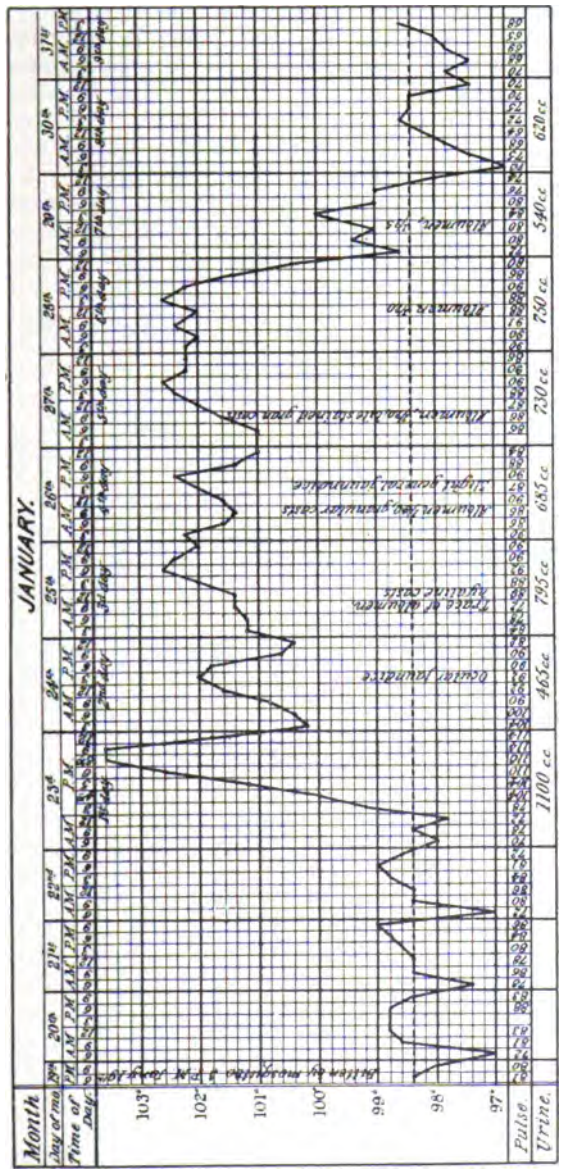


CHART V.—Yellow fever produced by the bite of *Culex fasciatus*. Period of incubation, 3 days 23½ hours.

jaundice was quite noticeable on the afternoon of the second day. Some jaundice of the face and anterior region of the chest was seen on the fourth day. Many bile-tinted granular casts were present in the urine on the third day and thereafter until the eleventh day. The albumin reached 1/15 by volume on the sixth day, disappeared on the twelfth day. (Chart V.) The subject has been in strict quarantine for the period of sixty days prior to inoculation.

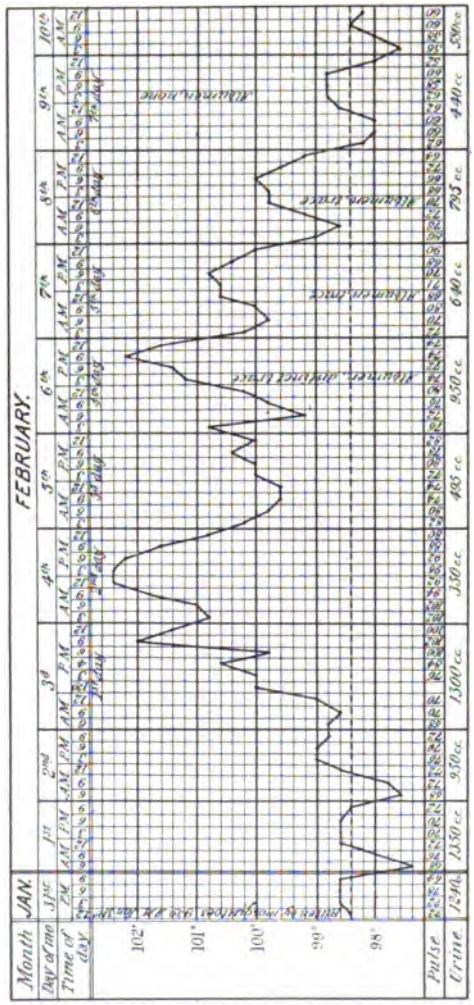


CHART VI.—Yellow fever produced by the bite of *Culex fasciatus*. Period of incubation, 3 days 2½ hours.

CASE VI.—C. W., American, non-immune, aged twenty-seven years, with his full consent was at 9.30 A.M., January 31, 1901, bitten by two

of the three mosquitoes that had been applied to the foregoing Case V. The interval that had elapsed since their contamination was, therefore, fifty-one days. The subject remained well until 12 o'clock noon February 3d, when he complained of heaviness in his legs and some supra-orbital pain. His temperature at this hour was 99° F. and pulse 70. At 1.30 P.M. it had risen to 100° F., and at 5 P.M. to 100.6° F. and pulse to 84. The primary rise of fever, which was somewhat fluctuating in character, did not reach its height until at the end of twenty-four hours—noon, February 1st—when the temperature was 102.4° F. and pulse 92. The facies was now suggestive of yellow fever. Remission occurred at the end of forty-five hours and lasted for about one day. The secondary rise was slight in character, the temperature falling to normal on the morning of the sixth day. The case was very mild in character. Albumin appeared at the end of seventy-five hours (beginning of fourth day); it never amounted to more than a distinct trace and disappeared on the eighth day. There was no ocular jaundice, and although the gums were injected and swollen there was no hemorrhage at any time. The patient perspired freely throughout the attack. Convalescence was rapid. The subject had been in quarantine for the period of six days prior to inoculation. (Chart VI.)

CASE VII.—J. H., American, non-immune, aged twenty-six years, in quarantine since December 20, 1900, with his full consent was bitten at 11 A.M., February 6, 1901, by the same two mosquitoes that had, six days previously, bitten Case VI. Fifty-seven days had therefore elapsed since these insects had been contaminated by biting a case of yellow fever. He remained well until 12 o'clock noon February 9th, when he experienced slight chilly sensations, accompanied by yawning. At this hour his temperature was 99° F. and pulse 72. At 3 P.M., temperature 98.8° F., pulse 72. Says that he feels out of sorts, but has no headache. At 5.30 P.M. his temperature was 100.6° F., pulse 78. He was not seen until 7.30 P.M., when he complained of backache and severe general headache, more intense through the frontal region. Eyes much injected, photophobia very marked, face flushed. He was stretching and yawning constantly. Complained of nausea and vomited a small quantity of partially digested food. The height of the primary fever was reached at 3 P.M., February 10th—*i. e.*, twenty-two hours after the commencement of the attack—when the temperature was 102.8° F. and the pulse 98. Remission of the fever to 99.4° F. and pulse to 74 occurred at 6 A.M. February 11th, making the duration of the primary paroxysm thirty-six hours. Twenty-four hours after the remission had occurred the temperature had risen to 102.4° F., with a pulse of 70. The fever continued to steadily increase until midnight February 12th, when a temperature of 105° F. was recorded, with a pulse of 90. The subsequent course was that of a case of severe yellow fever. Slight oozing of blood from the gums occurred as early as the third day. Ocular jaundice, beginning on the third day, became later very distinct and was associated with general jaundice. Albumin, however, did not appear until the sixth day. The fever subsided on the ninth day, and was followed by a slow convalescence. The subject

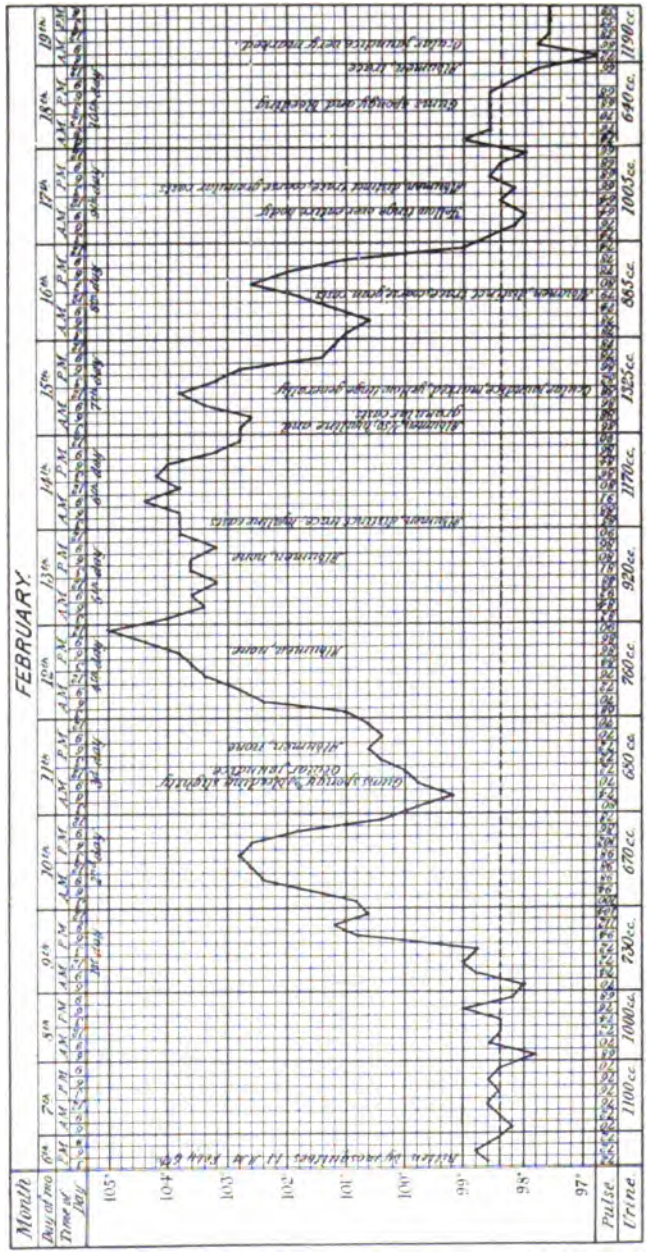


CHART VII.—Yellow fever produced by the bite of *Culex fascinatus*. Period of incubation, 3 days 6 hours.

had been in strict quarantine for a period of seventy-eight days prior to inoculation. (Chart VII.)

CASE VIII.—C. S., American, non-immune, aged twenty-eight years, in quarantine since January 13, 1901, with his full consent was bitten at 2 P.M.,

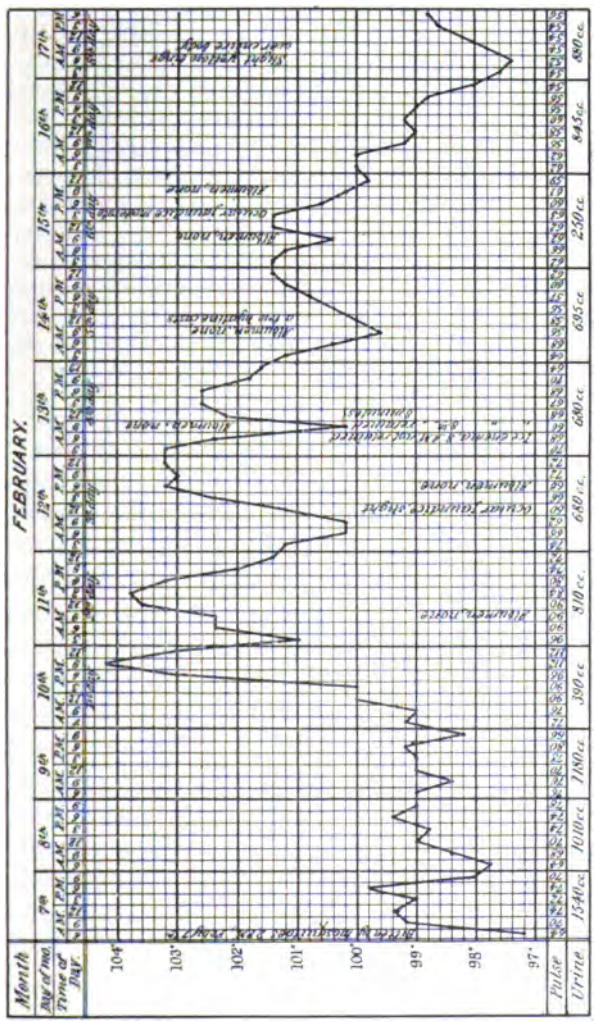


CHART VIII.—Yellow fever produced by the bite of *Culex fasciatus*. Period of incubation, 2 days 22 hours.

February 7, 1901, by three mosquitoes that had been contaminated sixteen days previously by biting a fatal case of yellow fever on the second day of the disease. (Chart VIII.)

The subject remained well until the early afternoon of the third day, February 10th. He ate his dinner at noon with good appetite. At 1 P.M. his temperature was 100° F., pulse 90. Frontal headache was now complained of. This became rapidly more marked, and pains in the limbs were also present. Three hours later, 4 P.M., the fever had risen only one-fifth of a degree, but at 6 P.M. it had reached 103° F. and pulse 96. At this hour he had severe headache and backache, with general pains over the body. The facial expression was now characteristic. Eyes brightly injected; photophobia well marked, and face decidedly congested. At 9 P.M. temperature was 103.2° F., and pulse 112. The skin was moist. Remission occurred at 6 A.M., February 12th, forty-one hours after the commencement of the febrile paroxysm. The secondary fever, which was moderate in character, lasted four days, the fever subsiding on the seventh day. Ocular jaundice was slight. A few hyaline casts were present on the third and subsequent days, but no albumin was found until 1 P.M., February 18th—that is, thirty-six hours after the fever had subsided. It was present as a distinct trace in all specimens examined until 3 P.M., February 23d. Convalescence was rapid. The subject had been in quarantine for a period of twenty-five days prior to inoculation.

The foregoing cases of experimental yellow fever (Cases V., VI., and VII.) are, we think, of especial importance as showing the length of time during which the mosquito may remain capable of conveying the infection. In previous papers we have reported six cases of yellow fever produced by the bites of mosquitoes at intervals varying from twelve to twenty-four days after the contamination of the insects. In the cases here reported the periods intervening between the contamination of the insect and the production of the disease were much longer, viz., thirty-nine, fifty-one, and fifty-seven days respectively. As one of these insects lived until the sixty-ninth and the other until the seventy-first day after contamination, we have for the first time an explanation of the fact—several times noted in the literature—that the contagion of yellow fever may cling for several months to a building that has been vacated by its occupants, or to the infected area of a town, even though this latter has been entirely depopulated. These particular insects, also, were contaminated at a later stage of the disease than in any of our other cases—*i. e.*, on the third day and during the secondary rise of the fever following a complete intermission in the temperature. We have, therefore, been able to demonstrate that the parasite is present in the general circulation both after and before the stage of remission. How much later in the disease the parasite may still be found

—a matter of much interest and importance—the observations thus far made do not determine. Although the three mosquitoes applied on the third day, as above stated, acquired the parasites and were able to infect three individuals with yellow fever, a single mosquito applied to the same case of yellow fever on the fourth day of the disease failed to obtain the parasite, as shown by the negative result following its bite forty days after contamination. That not all mosquitoes become infected, however, with the parasite by biting yellow fever patients is shown by several observations made by us. We submit only one:

J. W., American, non-immune, was with his full consent on January 25, 1901, bitten by twelve mosquitoes—*C. fasciatus*—that had been fed on a case of mild yellow fever—Martinez by name—on January 3, 1901, within eight hours of the commencement of the attack. Although these mosquitoes had been kept at summer temperature for twenty-two days, the result of the experiment was entirely negative. That the parasites were present in Martinez's blood at the end of twenty-four hours was fully shown by the effect produced by injecting 2 c.c. of his blood, drawn at this time, beneath the skin of Case I. of this report.

Observations such as the foregoing would indicate that the mosquito at certain periods of the disease may fail to obtain the parasite, owing to its absence at that particular time from the capillary circulation.

Concerning the matter of the propagation of yellow fever by other species of culex than *C. fasciatus*, we have only one negative observation to record of an individual bitten by five *C. pungens* that had been contaminated by biting a case of yellow fever nineteen days previously. To a single negative experiment such as this no importance can be given, so that this question must be left for future observations to determine. Touching the subject of the possible transmission of the parasite to the daughter insect by means of an infection of the ovum, we have, also, but a single observation to record. In this case the bites of fourteen mosquitoes, hatched from the ova of a mosquito—*C. fasciatus*—that had already shown itself capable of conveying the disease, were followed by an entirely negative result.

Including the cases heretofore reported by us, we have thus far succeeded in conveying yellow fever to twelve individuals by means

of the bites of contaminated mosquitoes, and to four other persons by subcutaneous injection of blood taken from cases of this disease —a total of sixteen cases. While ordinarily so small a number of cases would not be sufficient to enable one to arrive at definite conclusions concerning the general character and course of an acute infectious disease, the conditions under which the majority of these cases were observed were such as to give us valuable data concerning two matters of very great practical importance in connection with this disease, viz.: the period of its incubation and the difference in degree in the character of its attacks. Further, as these cases were kept under constant observation, even from the time of inoculation, we are not only able to report upon the earliest premonitory symptoms, but also to give the primary temperature-curve, and, in addition, to note the time of appearance of albumin in the urine, all of which are of interest in the clinical history of yellow fever.

Period of Incubation. The accurate determination of the period of incubation of any of the acute infectious diseases is always a matter of scientific interest. If the disease is one which, like yellow fever, is of exotic origin and whose importation is liable to give rise to a wide-spread epidemic, then the determination of its incubative stage becomes of the highest practical importance. This importance, as a question of public hygiene, is increased if, as recent observations would seem to indicate, the importation of this disease is brought about only by the sick individual and not by his baggage or clothing. While the older authors were willing to prolong the period of incubation of yellow fever to two or three weeks or even longer, the tendency of physicians at the present time is to shorten this stage to about five days. Reference to a few of the later textbooks on the practice of medicine will sufficiently indicate this. Davidson in Allbutt's *System*[1] puts down the period of incubation as "ranging between twenty-four hours and four or five days." Stevens[2] says that it may vary from "a few hours to a week." Osler[3] says that the "period of incubation is usually three or four days, but it may be less than twenty-four hours or prolonged to seven days." According to Tyson,[4] "yellow fever has a period of

[1] A System of Medicine, London, 1897, vol. ii. p. 394.
[2] Practice of Medicine, Philadelphia, 1898, p. 286.
[3] The Practice of Medicine, New York, 1899, p. 185.
[4] Practice of Medicine, Philadelphia, 1900, p. 85.

incubation of from twenty-four hours to five days, very rarely exceeding the latter." Sternberg[1] says that this period "does not usually exceed four or five days, and may be less than twenty-four hours." Carter,[2] in a recent valuable paper, gives the results of his studies on the period of incubation of yellow fever, based on observations extending over a considerable number of years. Under Class III. of his observations, which are the most valuable, he includes "those persons who, living in a clean environment, go into an infected one, stay only a short time, and then return to a clean environment, where they remain until the fever develops." Of twelve cases thus accurately observed by himself the incubative stage is as follows:

2	cases	with	3	days'	incubation.
6	"	"	3+	"	"
2	"	"	4	"	"
1	"	"	4½	"	"
1	"	"	5¾	"	"
12					

The following table gives the result of our observations in sixteen cases of experimental yellow fever:

TABLE I.—PERIOD OF INCUBATION OF EXPERIMENTAL YELLOW FEVER.

No. of cases.	Date of inoculation.	Method of inoculation.	Date of commencement of attack.	Incubation.
1	2 P. M., Aug. 27, 1900	Mosquito.	9 A. M., Aug. 31, 1900	3 days 7 hours.
2	11 A. M., Aug. 31, "	"	1 P. M., Sept. 6, "	6 " 2 "
3	2 P. M., Dec. 5, "	"	11.30 P. M., Dec. 8, "	3 " 9½ "
4	4 P. M., Dec. 8, "	"	9 A. M., Dec. 14, "	5 " 17 "
5	10.30 A. M., Dec. 9, "	"	9.30 P. M., Dec. 12, "	3 " 11½ "
6	4.30 P. M., Dec. 11, "	"	12 M., Dec. 15, "	3 " 19½ "
7	12 M., Dec. 21, "	"	11 A. M., Dec. 25, "	3 " 23 "
8	11 A. M., Dec. 30, "	"	10.30 A. M., Jan. 3, 1901	3 " 22½ "
9	11 A. M., Jan. 4, 1901	Blood injection.	9 A. M., Jan. 8, "	3 " 22 "
10	9 P. M., Jan. 8, "	" "	9 A. M., Jan. 11, "	2 " 12 "
11	3.30 P. M., Jan. 19, "	Mosquito.	3 P. M., Jan. 23, "	3 " 23½ "
12	1 P. M., Jan. 22, "	Blood injection.	9 A. M., Jan. 24, "	1 " 19 "
13	12.15 P. M., Jan. 25, "	" "	1.15 P. M., Jan. 28, "	3 " 1 "
14	9.30 A. M., Jan. 31, "	Mosquito.	12 M., Feb. 3, "	3 " 2½ "
15	11 A. M., Feb. 6, "	"	5 P. M., Feb. 9, "	3 " 6 "
16	2 P. M., Feb. 7, "	"	12 M. Feb 10, "	2 " 22 "

The average period of incubation of these sixteen cases, embraced in Table I., will be found to be eighty-seven and one-quarter hours, or

[1] Buck's Reference Handbook of the Medical Sciences, 1889, vol. viii. p. 58.
[2] The Period of Incubation of Yellow Fever, New York Medical Record, March 9, 1901.

three days, fifteen and one-quarter hours. If we separate the twelve mosquito infections from the four cases produced by the injection of blood, we have for the former a period of incubation of ninety-four hours, or three days and twenty-two hours, and for the latter an incubative stage of sixty-seven and a half hours, or two days, nineteen and a half hours. The average period of incubation, therefore, in the cases brought about by subcutaneous injection of blood was shorter by twenty-six and a half hours than those occasioned by the mosquito's bite. By the former method this stage varied from forty-three hours to ninety-four hours, while in the mosquito infections the shortest incubative period was seventy and the longest one hundred and forty-six hours. If we accept those cases produced by the mosquito's bite as the usual method of propagation of this disease, it will be observed that of the twelve cases one occurred on the third day; nine on the fourth day; one on the sixth day, and one at the beginning of the seventh day after incubation.

While our results, therefore, confirm the statement of later writers that the period of incubation of yellow fever does not usually exceed four or five days, they also seem to indicate very plainly that this stage may be prolonged more frequently, perhaps, than had been supposed.

In 16.6 per cent. of our cases the period of incubation exceeded the usual quarantine period of five days. If we add Carter's cases to those observed by us we find that of twenty-four cases the period of incubation exceeded five days in three, or 12.5 per cent. We will not further dwell on this subject than to remark that Cases 2 and 4 of Table I. could have passed quarantine on the morning of the sixth day after inoculation, with a clinical thermometer under the tongue, without exciting any suspicion by reason of the presence of fever.

Character of the Attack. We desire to call attention particularly to the difference in the degree of severity of the attack as shown by our experimental cases. Like all of the other acute infectious diseases, we have reason to expect that yellow fever will affect different individuals according to their individual susceptibilities, and hence that we will encounter mild as well as severe cases. The results which we have obtained confirm this expectation. Based upon the

character of the attack, the twelve cases due to mosquito inoculation may be divided as follows:

Severe	2
Moderately severe	6
Mild	3
Very mild	1
	12

The four cases produced by the injection of blood gave the following result:

Severe	1
Moderately severe	2
Mild	1
	4

Thus the cases which were mild or very mild in character constituted 33 per cent. of those infected by the mosquito's bite, and 25 per cent. of those produced by blood injection. It is to the diagnosis of the former cases that we desire to direct especial attention. To one familiar with yellow fever, or even to one unfamiliar with its clinical features, the diagnosis of our severe and moderately severe cases should have presented no difficulty. The sharp headache and backache, the characteristic facies, the ocular jaundice, together with the presence of albumin in the urine, except in one case to be hereafter referred to, with the negative result of a blood examination, would have been a sufficient complex of symptoms to have rendered the diagnosis tolerably certain. Even in our three "mild" cases, were the physician on his guard and acquainted with the temperature-curve and pulse from the very onset of the attack, and, beside, careful in the testing of each specimen of urine passed, a diagnosis of yellow fever could have been made with reasonable probability. We believe, however, that in the ordinary course of events, where there was no reason to suspect the presence of yellow fever, the average practitioner would have probably failed to appreciate the true nature of these attacks. Such was the admission which we ourselves were compelled to make, although in constant attendance and thoroughly acquainted with these cases from their very beginning. The short duration of the primary fever, in one

instance, the rapid amelioration of the earlier symptoms in all, the absence of albumin during the first three days, or its presence, as a mere trace in certain specimens of urine, followed by its absence in succeeding specimens; the slight icteroid hue of the conjunctiva—to be obtained only in a certain light and then doubtfully—all served to render a positive diagnosis exceedingly difficult. Several physicians who saw these milder cases at our request readily acknowledged the improbability of a correct diagnosis being made in the absence of the complete data which we were able to furnish concerning them. In the one case which we have classed as "very mild" yellow fever we believe that the matter of a correct diagnosis would have been in the highest degree improbable. The attack consisted of a single paroxysm of thirty-three hours' duration, during which the temperature only reached 101° F. for a period of six hours. It is true that albumin was found in the urine at the end of thirty-seven hours, but the quantity was exceedingly small and only to be detected by the most delicate testing. It was only present in one of the two specimens passed on the third day. A slight trace was present in a specimen passed at 9 A.M. of the fourth day and in that passed at 4.40 P.M. of the fifth day. Intervening specimens of urine, several in number, contained no albumin. A well-marked papular eruption, which appeared on the fourth day of the disease, and which was confined to the trunk and arms, would hardly have rendered the diagnosis easier. We suppose that during the prevalence of an epidemic of yellow fever a physician who was thoroughly acquainted with the several types of this disease would probably class this case as one of extremely mild yellow fever, with a wide margin for doubt. Under all other circumstances we feel confident that cases of this character would escape diagnosis. That cases of mild yellow fever may and do serve as foci for the development of other cases, our own observations demonstrate, since we have been able to propagate the disease from one such mild case by means of the bites of contaminated mosquitoes, and from another case of like character by the subcutaneous injection of 2 c.c. of blood.

The Onset and Premonitory Symptoms. Of the twelve cases produced by mosquito inoculation, the onset was sudden in two and gradual in ten. In both of the former the attack occurred during the night, the patient, also, in both instances being awakened by

the occurrence of a decided chill. In one of the two cases of sudden onset the subject complained of slight supraorbital headache during the afternoon preceding the attack. Of four cases produced by the injection of blood the onset was sudden in one—the only case marked by a chill—and gradual in three. The attack in all of these blood cases began during the daytime. As writers generally state that in yellow fever the chances of infection are greater during the night, we have thought that, perhaps, the time of inoculation of our experimental cases, which was during the day (except in one instance), might have had some influence upon their occurrence, as a rule, during the daytime. If the hour of inoculation in all of our cases should have taken place at about sunset, then with the same period of incubation seven, or 43 per cent., would have experienced their attacks at night.

Of the thirteen cases in which the onset was gradual—by mosquito inoculation, 10; by blood injection, 3—frontal headache, the pain being referred to the supraorbial region, and extending into the temporal region, was the most frequent premonitory symptom. It was present in ten and absent in three cases. This symptom preceded the attack in these cases at intervals varying from two to forty-eight hours. In two cases no premonitory headache was complained of, while in one case occipital headache preceded the onset by twenty-four hours and continued to be of this character throughout the attack. Dizziness was complained of by three of the gradually developing mosquito cases, and a sense of weight in the lower extremities by two others belonging to this group. All of the cases of gradual onset (thirteen in number) complained of lassitude and want of appetite, on which account all took to their beds prior to the onset of fever. Ten of these individuals complained of slight sensations of chilliness—generally confined to the lower extremities—at the beginning of the attack, while in three this symptom was entirely absent. In our experimental cases, therefore, frontal headache and muscular debility were the most frequent and prominent premonitory symptoms. After the attack had developed the symptoms corresponded to those described at length by various writers and with which all are familiar—except that black vomit did not occur in any of our cases.

The Fever. As we have prepared charts of our several cases of

experimental yellow fever, from which all the data concerning temperature and pulse can be obtained, it will not be necessary for us to make extended remarks under this heading. Medication being practically *nil* in our cases, both temperature-curve and pulse can be accepted as faithfully representing what normally takes place in an attack of this disease. Where ice-water enemata or cold sponge baths were used by the attending physician this is noted on the chart. It should also be remembered that our patients were put to bed at the very first manifestation of the disease, and carefully transported to the yellow fever wards on the very same beds which they had occupied in camp. This probably had some effect upon the subsequent course of the fever. The record of temperature taken every three hours from the time of inoculation enables us to give the complete curves of both the primary and secondary febrile paroxysms. Our charts, therefore, differ considerably from those given by the various writers on yellow fever in that they round out, as it were, the primary stage more fully. An examination of these charts will show that although the primary rise of temperature is tolerably abrupt and reaches its height within a comparatively short time, it does not reach its maximum so quickly as the description of writers would seem to indicate. The tri-hourly record in ten of our mosquito inoculations shows that this period of primary rise varies from twelve to twenty-four hours. In three cases it was twelve hours; in two, fifteen hours; in one, fifteen and a half hours; in one, twenty and a half hours; in one, twenty-two and a half hours, and in two, twenty-four hours. The average period for the ten cases was, therefore, a fraction over sixteen hours.

In striking contrast to these was the short period of the primary rise of temperature in the four cases produced by blood injection. In these it varied from two and a quarter to nine hours, the remaining two cases giving six and seven hours respectively, the average for the four cases being only six hours. In all of the twelve cases due to mosquito inoculation the primary rise of temperature was followed by a distinct remission or intermission which was generally reached within forty-eight hours. The same remission was present in three of the four cases produced by blood injection. We are able to give the duration of the primary paroxysm accurately in the ten cases produced at Camp Lazear by the bites of mosquitoes, viz.:

1 case	33 hours.
1 "	33½ "
1 "	36 "
1 "	39 "
1 "	41 "
3 cases	45 "
1 case	52 "
1 "	60 "

The average duration of these ten cases was forty-three hours. In the three cases caused by the injection of blood the length of the primary paroxysm was twenty-four hours in two cases and thirty-six hours in one case—the average being twenty-eight hours. We may, therefore, say that not only the average period of incubation, but also the primary rise of temperature, as well as the length of the first febrile stage, were all shorter in the cases produced by blood injection than in those due to the mosquito's bite. Of the twelve cases due to the latter mode of inoculation, the first febrile stage was followed by an intermission in two and a remission in ten cases. Of those produced by the injection of blood, three showed a distinct remission and one no intervening fall of temperature. The duration of this intermission varied from three to twenty-seven hours. This was followed by a second febrile stage or paroxysm in eleven of the twelve mosquito inoculations, and in three of the four cases due to injection of blood. The duration of this second febrile paroxysm was from two to five days.

Experimental yellow fever, then, as we saw it at Camp Lazear, consisted of a primary and secondary febrile paroxysm with an intervening remission or intermission—more frequently the former. The secondary was much longer than the primary febrile stage.

In one of our mosquito inoculations a relapse occurred on the ninth day of the disease, and was characterized, also, by two febrile stages with an intervening remission. There were present headache and backache, with injection of the eyes and face, together with hemorrhage from the gums, as had been observed in the primary attack.

The want of correlation between temperature and pulse (Faget's law), upon which clinicians rely as an important diagnostic sign, was seen, as a rule, in our experimental cases—*i. e.*, after the passage of the first febrile stage. In one case produced by the injection of blood Faget's law was not complied with.

The Urine. We have confined our examination of the urine largely to testing for the presence of albumin and to the ordinary microscopic examination of this fluid. Heat and nitric acid was the method used in all cases for the detection of albumin, the specimen having first been carefully filtered.

Under this heading we desire to speak only concerning the presence of albumin. All writers dwell on the importance of a careful examination of the urine in suspicious cases of fever, since the presence of albumin in the urine is such a constant sign in yellow fever. Guitéras, who has had a large experience with this disease, says: "The albumin appears in the urine usually on the third or fourth day of the disease. It may be very transient. In many mild cases the albumin is present only in the urine passed in the evening of the third or fourth day. In many cases it is only a trace." We may say that the results obtained from an examination of the urine of experimental yellow fever accord, for the most part, with the statement above quoted.

In our earlier cases we did not examine for albumin until the onset of the attack. In our last eight cases (those embraced in this report) we examined daily specimens from the time of inoculation until the attack began, and thereafter we endeavored to examine every specimen passed by the patient. Table II. gives the results obtained:

TABLE II.

Cases.	Mode of inoculation.	Albumin during period of incubation.	Time of appearance of albumin during the attack.	Time of disappearance of albumin dating from appearance.	Maximum quantity.	Remarks.
1	Mosquito.	None.	42 hours.	10th day.	8/10 by vol.	
2	"	"	25 "	11th "	3/10 by vol.	
3	"	"	82½ "	15th "	2/10 by vol.	
4	"	"	48 "	5th "	Distinct trace.	
5	"	"	64½ "	4th "	Light trace.	
6	"	"	43½ "	3d "	Distinct trace.	
7	"	"	37½ "	8th "	" "	
8	"	"	43 "	9th "	1/40 by vol.	
9	"	"	42 "	12th "	1/20 by vol.	
10	"	"	75 "	8th "	Distinct trace.	Albumin did not appear till 36 hours after fever had subsided, and persisted for 5 days.
11	"	"	106 "	15th "	1/40 by vol.	
12	"	"	None.	.....	1/20 by vol.	
13	Blood.	None.	61 hours.	13th day.	Distinct trace.	
14	"	"	17 "	12th "	" "	
15	"	"	57 "	9th "	" "	
16	"	"	18½ "	15th "	1/10 by vol.	

An examination of the cases presented in this table will show that of the twelve mosquito inoculations the earliest appearance of albumin was at the beginning of the second day in one case; during the second day in five; at the end of the second day in one; during the third day in one; during the fourth day in two; during the fifth day in one; while in one, a well-marked case, no albumin could be detected till thirty-six hours after the temperature had reached the normal—*i. e.*, till the second day of convalescence. It then persisted during five days. In all twenty-three specimens of urine were examined in this case during the six days of fever, but with an entirely negative result as regards the presence of albumin. An occasional hyaline or fine granular cast could be found in the majority of these specimens. We submit this case of experimental yellow fever as one of especial importance from the clinical standpoint, since the absence of albumin during the attack would have probably led to an error in diagnosis. How very exceptional such cases may be we have no means of knowing.[1]

It will be observed that the quantity of albumin present in this series of cases was very moderate, except in Cases 1 and 2 of Table II. These cases were the only two of the sixteen that were not placed in bed from the very beginning of the attack. In the remaining fourteen, all of whom were kept at absolute rest during the whole period of the fever, the amount of albumin was small in six and insignificant in eight. We are inclined to believe, therefore, that both the course of the fever as well as the quantity of albumin were favorably affected by the early enforced rest of our patients.

In conclusion, we desire to invite attention to two matters which we consider of considerable importance in connection with the possible importation and propagation of yellow fever. First, we believe that the facts herewith presented indicate that the period of incubation of yellow fever occasionally exceeds the quarantine period of five days, and that, although exceptional, this must not be left out of consideration. Secondly, that our observations emphasize anew the importance of the recognition by the profession of mild and very mild cases of yellow fever. Guitéras[2] says: "I cannot insist too

[1] It is of interest to note that this particular individual, two weeks prior to successful inoculation and while in quarantine, had an intermittent albuminuria which lasted three days.

[2] Report of the U. S. Marine Hospital Service, 1897–98, vol. xxvii. p. 300.

much upon the importance of the diagnosis of the first case of yellow fever in a locality." He adds: "Undoubtedly the cause of the epidemic of yellow fever is to be found in the introduction into a community of cases that are not suspected to be yellow fever." In the light of our investigations we feel constrained to remark that the failure to detect cases of mild yellow fever has been, we believe, the most important factor in the development of the theory of the propagation of this disease by fomites.

DISCUSSION.

DR. STERNBERG: The demonstration of the method in which yellow fever is transmitted makes clear to us the apparently contradictory facts with reference to the etiology of this disease. For instance, it was known that ships arriving at New Orleans from Havana without any cases of yellow fever on board would be unloaded by stevedores, some of whom would be taken ill with yellow fever three or four days afterward, and in the course of twelve or fourteen days other cases would crop up. It is now clear why they have succeeded in New Orleans and other ports in disinfecting such ships by sulphur dioxide. Supposing the cargo to be infected it was difficult to understand how the burning of sulphur in the hold could secure disinfection. It is easy to understand now, however, since we know that the infection was carried by mosquitoes, and not by the cargo. As they were hanging about on the sides and ceilings of the hold it was easy to destroy them with sulphur dioxide.

Then again, some of my own experiences with yellow fever are now made clear for the first time. In 1873, while at Fort Barancas, a ship with yellow fever aboard passed the fort, but there was no communication with her. Within two weeks several cases of yellow fever appeared in different localities, and the only explanation was based upon the theory that something had washed ashore from the ship and lodged on the beach. There was a similar occurrence at Governor's Island in 1870; something came from the ships anchored off shore and we had an outbreak of yellow fever. Again we thought that something had floated ashore. It is now plain, of course, that in both instances mosquitoes carried the infection from the ship to the shore. I consider the experimental demonstration made by Reed and Carroll as absolutely complete and satisfactory.

As long ago as 1880, at Vera Cruz, I attempted to find out whether there was anything in the blood of yellow fever patients that would give the disease to others. At that time there was only one case of yellow fever in the hospital and that in an advanced stage of the disease. My assistant drew from the patient's circulation a syringeful of blood and injected it under

the skin of a non-immune, but there was absolutely no result. I had demonstrated that yellow fever could not be transmitted to the lower animals by blood injections, which I had repeatedly tried upon dogs, guinea-pigs, etc. In the blood examinations made by Guitéras and myself there was also a failure to demonstrate any organism. So when Dr. Reed went to Cuba I told him that one of the things to determine was whether there was anything in the blood by which the disease could be transmitted. By his very skilfully conducted experiments, and with the aid he received through General Wood and the American soldiers and others, who volunteered for the experiment, he has demonstrated that there is something in the blood of yellow fever patients that conveys the disease to others.

I have criticised the claims of Finley simply because his own report did not give support to his theory. We can see now why he failed, he did not keep his mosquitoes long enough. Reed and Carroll have shown that mosquitoes do not transmit the disease when kept only for two or three days, but that it requires twelve days after they have filled themselves with blood from a yellow fever patient before they can communicate the disease to a non-immune person.

I can only say further that I congratulate these gentlemen most heartily on their success. It shows how long a journey we must often take before arriving at the truth. I spent four long summers in Cuba and Brazil in investigations relating to the etiology of this disease, and the results were negative, but perhaps I was preparing the way for this success; and now that the presence of the infectious agent in the blood has been determined and the mode of transmission demonstrated, we have reason to believe that the parasite will soon be discovered, unless, indeed, it should prove to be ultra-microscopic.

Dr. Welch: I would like to say that the fact has not been brought out by Dr. Reed this morning that none of these patients died, a piece of good fortune, for these experiments were undertaken with a full sense of responsibility. It should also be said, and Dr. Reed has referred to it elsewhere, that these young men, American soldiers, unwilling to accept a cent of pay for their services, submitted themselves for this experimental work, and I think they should be known in the history of the army as well as in medical circles as true heroes.

SEPTIC INFECTIONS THROUGH LESIONS OF THE STOMACH AND DUODENUM.

By WALTER B. JAMES, M.D.,
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It is generally assumed and stated that septic poisoning rarely takes place through lesions of the stomach and duodenum. Influences that would operate against such an occurrence are, first, the acidity of the gastric contents and the inhibiting effect which this reaction possesses toward bacterial growth and activity; and, second, the very effective protective mechanism against the inroads of bacteria which is supposed to reside in the liver and to operate upon any such elements that may find their way into the portal stream.

I leave out of consideration the local inflammatory complications which fairly often occur in connection with gastric lesions, such as abscess or circumscribed peritonitis, and refer only to general septic poisoning without such definite local manifestations.

The occurrence in the practice of the writer of several cases in which the clinical picture, and in some instances the results of the postmortem examination, pointed to the existence of septicemia, mild or severe, where it seemed probable that the portal of entry for the infecting organisms had been lesions of the stomach or duodenum, attracted attention to this point and suggested an inquiry into it. The frequency of cases of septicemia, in which the somewhat humiliating admission must be made that they are of unknown origin or cryptogenetic, and this occasionally even after a careful postmortem examination has been made, justifies an attempt to throw light upon even a small group of them.

Within a few years a multitude of observations have established the fact that the bacterial flora of the stomach is an extensive and varied one, and that a large number of micro-organisms may be found there in an active state and able to exhibit their peculiar properties.

Sternberg[1] many years ago concluded that it was possible for bacteria taken into the mouth to escape the effect of the gastric juice and pass into the duodenum.

Strauss and Wartz[2] found that fresh gastric juice contained many living bacteria; that they diminished in number until the eighth day, after which no growth could be found; and finally, that a culture of tubercle bacilli after being exposed to the action of normal gastric juice for six hours was capable of producing tuberculosis in guinea-pigs.

Miller[3] found that bacteria could live for from six to eight hours in the stomach of a healthy dog; that the bacteria swallowed at the commencement of a meal escaped the action of the gastric juice and passed into the duodenum, but that of those taken two or three hours later at the height of digestion only the most resistant varieties succeeded in accomplishing this.

Weiss[4] says that many species of bacteria can be found in the stomach of a cat even at the height of digestion, and are then capable of exerting their special influence.

Gillespie[5] finds that the inhibitory action of hydrochloric acid commences from half to three-quarters of an hour after a meal; that hydrochloric acid combined with proteid has only a feeble bactericidal power; that even at the height of digestion only the most susceptible micro-organisms are destroyed, while many others are only inhibited; that the former view that antisepsis was an important function of gastric juice has now been definitely disproved.

Cushing and Livingood,[6] in a recent interesting investigation, conclude as follows: Probably the microbes found in the alimentary canal have entered by the mouth and are not necessary to life. Except the bacillus coli communis, which they regard as normal, the bacteria found there are accidental and depend upon the number and varieties introduced with the food, and that the gastric juice is not an efficient antiseptic, even at the height of digestion; that some pathogenic varieties, especially the streptococcus pyogenes, readily escape the antiseptic action of the secretion. At the terminal stage of digestion, or after a prolonged fast, however, it is difficult to recover any micro-organisms from the mucous membrane of the stomach, duodenum, or even jejunum, but that the number and variety of the micro-organisms increase as one proceeds along the intestines until the ileocecal valve is reached.

In a very recently published thesis Coyon[7] reports the results of a searching investigation into the microbial flora of the stomach. His conclusions do not differ materially from those given above. He isolated thirty varieties of bacteria from this organ in an investigation of the stomach contents of twenty patients, some of whom were the subjects of dyspeptic troubles, others were in good health.

Thus there is abundant evidence proving that the stomach and duodenum practically at all times contain large numbers of the bacteria that are taken with the food and in an active state, each capable of exerting its peculiar influence. We have present, then, in this organ the conditions needed to bring about a septic poisoning should a solution of continuity take place in the mucous membrane.

Of all the organs in the body none is more habitually abused than is the stomach, it being made the receptacle—often the unwilling receptacle—of all that the unreasonable palate of its owner forces upon it, and it is not at all to be wondered at that its maladies are so many and so frequent, and that so few persons escape them for any considerable length of time, and solutions of continuity in its mucous membrane are so often met with.

The recent very interesting investigations of Adami[8] and Ford[9] tend to indicate that bacteria are constantly in health being taken up from the alimentary canal, conveyed to the liver by the portal circulation, and there destroyed and got rid of. If their observations should be confirmed they would throw much light upon the problems under consideration, but would not render untenable the assumption that occasionally cases of sepsis might occur. Nature provides us with a protective mechanism against the ravages of the bacteria that surround us, but a mechanism that occasionally breaks down and becomes ineffectual, under which circumstances septicemia may occur.

There is a large amount of literature bearing upon the question of the penetration of the normal mucous membrane by bacteria and the existence of micro-organisms in normal organs and normal blood. Comparatively little is at hand upon the subject of the entry of bacteria into the body through the pathologic lesions of the gastro-intestinal tract.

Fischl[10] studied preparations from various organs of children that had died of septicemia and marasmus, and demonstrated the presence of staphylococcus pyogenes albus and streptococcus pyogenes through-

out the body. The cases had suffered from gastroenteritis, and the author believed that they died of septicemia, the portal of entry being the gastrointestinal lesion.

Siebourg,[11] in a dissertation upon cryptogenetic septicemia, claims that the portal of entry in many cases is the mucous membrane of the digestive tract.

The possibility that severe and even fatal septicemia may have its starting-point in an erosion or similar solution of continuity of the mucous membrane of the stomach is suggested by the following case:

The patient, Mr. F., aged fifty-six years, was seen on several occasions in consultation with Dr. Laneheart, of Hempstead, Long Island. He had been absolutely healthy and vigorous until about a year and a half before, when his health became not quite so good. He lost a little strength, looked paler than usual, and on one occasion fainted. There were a little nausea and vomiting. During this period he lost about thirty pounds in weight. No hemorrhage was noted. He then began to improve, and during the past summer his health had become much better. He recovered from his moderate anemia and looked perfectly well, although he was not quite so strong as formerly. During the past six months he was in good health, leading a vigorous out-of-door life, riding horseback and feeling absolutely well.

For about two weeks before the onset of his final illness he had not felt quite so well as formerly, but with no definite complaint.

May 7th. At nine o'clock in the morning he had a chill, following which the temperature rose to 104.5°. After this the temperature was very irregular, ranging from 100.5° to 103°. The pulse was rapid. There was no headache and no pain.

8th. In the afternoon there were two slight chills, following which the temperature rose to 105.5°.

10th. There is irregular fever, with excursions ranging from 102.2° to 105°.

11th. The temperature is about the same as yesterday. There is a little swelling and edema of the right forearm and the right lower leg, with yellowish discoloration of the skin, apparently due to septic thrombosis. The patient appears weaker, but still complains of no pain. There are no other symptoms.

12th. Examination of the blood shows no increase in the number of the leucocytes, but a large relative increase in the polymorphonuclear variety. This is considered to indicate an overwhelming septic poisoning, and an opinion is given that he is suffering from a cryptogenetic septicemia of great intensity. There are no malarial organisms in the blood. There is moderate delirium, very rapid pulse, very slight icterus. Temperature is still irregular as before, but the average is a little lower.

Physical examination shows moderate enlargement of the spleen. There are no other evidences of disease of any of the organs.

13th. He grew much weaker, became unconscious, fever persisted, and in the late afternoon he died.

On May 11th, two days before death, a specimen of blood was taken from a vein under antiseptic precautions and planted in blood-serum tubes. All showed pure culture of one of the pyogenic bacteria.

A postmortem examination was made six hours after death. The spleen was much enlarged, soft, pulpy, and deeply congested. The stomach showed very moderate dilatation; it contained a small amount of disintegrated blood; on the greater curvature at the junction of the middle and distal third and projecting into the cavity was a bright red mulberry-like tumor, about the size of an Italian chestnut, the surface of which was eroded and inflamed. There were no peritoneal adhesions or other evidences of inflammation outside the stomach. The other organs showed only the usual parenchymatous lesions generally associated with any acute infectious disease.

Cultures were taken from the various organs. From blood from the auricles and from the superior mesenteric artery a pure growth of staphylococcus pyogenes aureus was obtained; cultures from the other viscera showed only a growth of lactis aerogenes and bacillus subtilis, which were regarded as postmortem contaminations.

Microscopic examination of the tumor of the stomach showed it to be an adenoma, the mucous membrane covering the surface of which was acutely inflamed, eroded, and infiltrated throughout with the ordinary products of inflammation, while the solitary lymph nodules were much enlarged and in some places penetrated the mucous membrane so as to reach the surface.

The occurrence of an acute and overwhelming septicemia, in which the postmortem examination failed to reveal any port of entry for the infection excepting the above-mentioned tumor of the stomach, the surface of which was eroded and acutely inflamed, seemed to justify the conclusion that this was the original seat of the infection.

If a solution of the continuity of the gastric mucous membrane exposes the individual to danger of septic absorption, one would expect that evidences of such a complication would occasionally be present in ulcer of the stomach and in cancer in the same organ.

The occurrence of an irregular fever of varying degree and intensity has often been noted in cases of ulcer of the stomach. The usual explanations of this are that it is due to the reaction from the anemia which follows hemorrhage, or that it is due to some inflammatory complication, such as localized peritonitis or a local abscess, or to toxemia resulting from the disintegration of the blood poured out into the intestine. This elevation of temperature, however, occurs in a large number of cases in which a careful study of the clinical features

seems to justify the exclusion of any inflammatory sequence of the lesion. To explain the fever in every case on the ground of the loss of blood and the consequent anemia does not seem altogether satisfactory. It occurs occasionally in cases where the hemorrhage has been only slight or has not been present. It is absent from many of the cases where the hemorrhage is very profuse. The fever is often of much higher grade and more irregular in type than one would expect to find from a simple moderate loss of blood.

Fenwick,[12] in his recent treatise upon the ulcer of the stomach, speaks of this fever as belonging to the anemia, and states that it occurs most often and most markedly in persons who have been previously robust and in those who have bled only moderately. He says, however, that he has seen no reason to believe that pyemia ever occurs from absorption through the base of a gastric ulcer.

In the cases of ulcer of the stomach that have been studied by the writer, the fever, when present, has generally been irregular in type. It showed no characteristic periodicity, ranging from 100.5° to 106°. In some cases there was a moderate leucocytosis. This was not, however, believed to be of much diagnostic value, as in most of the cases the existence of hemorrhage would naturally have given rise to this condition. In several cases the fever was of hectic type. It was generally present during the period of activity of the ulcer, and subsided gradually, and entirely disappeared in convalescence. As one studies the temperature-charts in these cases the impression is obtained that it is an accidental feature of the disease and not an integral part of it.

From the following list of cases all have been excluded in which there were evidences of any complicating inflammation, such as peritonitis or abscess, or in which there seemed to be any other possible source of fever, such as pneumonia or bronchitis.

Of eleven cases of ulcer of the duodenum six presented an elevation of temperature. In three the fever was of low grade, but continued for several days; in two it did not rise above 100°; in one case to 100.5°. In the fourth case there was an irregular fever, lasting eight days, as high as 102.6°. The leucocyte count was on one occasion 12,000, on another 20,000. This patient died. The autopsy showed an ulcer of the duodenum. There was no recent peritonitis or evidence of local inflammation. There was a small superficial abscess in

one kidney, which was thought to be metastatic. In another case there was a continued irregular fever as high as 102.6°, lasting several days, and going on to recovery.

One hundred and seventeen cases of ulcer of the stomach were studied. Of these, thirty-three showed a tolerably marked irregular febrile movement, the temperature in all reaching as high as 101°. In fourteen cases the temperature reached 102°. A leucocyte count was made in only eight of this series; in four of them there was well-marked leucocytosis. Two of the fatal cases present enough features of interest to justify their presentation in abstract:

A woman of twenty-five years was admitted to the hospital, giving a history of previous good health. The day the patient was admitted she fainted, and then vomited a large quantity of blood. Three days after she passed blood from the bowels and vomited blood again. There was marked pain in the epigastrium; the hemorrhages continued at intervals of two or three days. The temperature was at first normal and then rose to 102.6°. She continued to present irregular fever—from 101° to 104°—having the type of hectic fever, which lasted for ten days, when she died. The general appearance of the patient did not indicate that the cause of death was the loss of blood. A postmortem examination disclosed the presence of a superficial ulcer situated upon the posterior wall of the stomach at the lesser curvature. No other lesions were found. There were no evidences of any complicating inflammation in the neighborhood of the ulcer. In this case no cultures from the organs were made.

The second case was as follows:

A female, aged thirty-one years, was admitted to the Presbyterian Hospital April 18, 1897, giving the following history: She has always been healthy and her habits have been good. She has had indigestion off and on for several years, with pain in the epigastrium after eating. The dyspepsia has been more severe during the past winter. With this exception her health has always been good. On the evening before admission she felt slight pain under the ensiform cartilage, and then vomited blood; the next morning the pain returned, and again she vomited blood; she has noticed no blood in the stools. On admission the temperature was 100.8°, pulse 92, respiration 20. The urine was normal. Physical examination showed the thoracic and abdominal organs normal, excepting slight tenderness in the epigastrium.

April 20th. Temperature was 100.5°. She has vomited a moderate amount of greenish fluid with foul odor, but no more blood. Temperature in the evening was 101.2°.

23d. There is no increase of the abdominal tenderness. She does not appear to be suffering from loss of blood. There is no marked pallor of the skin or mucous membrane; there is slight delirium.

24th. She passed two stools containing a moderate amount of tarry material. There is no vomiting; the delirium is more marked. Temperature in the morning 101°, in the evening 105.8°. There are no signs of any inflammatory process in the chest or abdomen.

25th. Delirium is very active. There are no movements from the bowels, nor is there vomiting; the general condition is unchanged. The temperature rapidly fluctuates between 104° and 107.5°; pulse, 130 to 160. There is no appearance of exsanguination; the pallor is not excessive, nor is there rapidity of respiration or air-hunger.

On the dext day, April 26th, the temperature continued high, pulse grew more feeble and rapid, and the patient died.

Unfortunately, it was not possible to perform a postmortem examination, but the appearance and general behavior of the case left a distinct impression that she was suffering from an intense acute infection.

In this series of cases no examination of the blood for bacteria was made. It is to be regretted that an examination of the blood was made in so few of these cases, but most of them occurred at a time when the blood was much less regularly and thoroughly studied than is the case now.

A study of the above series of cases has suggested the probability that septic poisoning does occur from time to time in ulcer of the stomach, that it may be one of the causes of the fever which is so often present, and that it may be an element of much importance in the clinical possibilities of this disease. Moreover, an investigation of a corresponding series of cases of gastric disorder, such as hyperchlorhydria, atonic dilatation, and other conditions more or less closely simulating ulcer of the stomach, but in which the final outcome indicated that this latter lesion had not been present, generally showed an absence of fever even of low grade. This has suggested the possibility that in a few of these puzzling cases where the differential diagnosis lies between gastric ulcer and severe functional gastric disturbance, a careful study of the temperature record may be of service in aiding the diagnosis, the presence of fever pointing to the existence of an organic lesion with loss of substance.

In cancer of the stomach, also, the presence of fever has been noted, many cases having been reported with temperature reaching a high point—104° or 105°—sometimes preceded by chills and followed by sweating.

In a recently published monograph by Osler and McRae,[13] fever was noted in about 50 per cent. of cases of cancer of the stomach. There were eight cases which showed an irregular hectic temperature. Two cases had chilly feelings, with a rise of temperature to 100° and 102°. Two others had definite chills with temperature of 103° and 104°. In the other two cases of highest temperature—103° and 104°—the autopsy failed to show a perforation.

In a series of thirty-six cases that have occurred in the Presbyterian Hospital in the past three years, eighteen, or exactly 50 per cent., have shown fever as high as 100°. In ten cases the course of the febrile movement was that of a hectic fever, and the history and clinical picture strongly suggest a septic process. In one of these cases there was a well-marked leucocytosis.

In this series, as before, I have omitted all cases in which the existence of any inflammatory complication was indicated.

In this disease also it seems possible that the presence of fever may be of service in aiding an early differential diagnosis from functional gastric disturbance.

In one case which is still under treatment, a woman of middle age gave a history of rather persistent dyspepsia with fairly marked loss of flesh. There were none of the physical signs of a stomach tumor, nor was there hematemesis, but an irregular febrile movement of very low grade, together with a well-marked leucocytosis, and for which no other cause could be discovered, helped to confirm the impression that she was suffering from cancer of the stomach rather than from functional disease, and this impression has been justified by the subsequent course of the disease and the continued absence of free hydrochloric acid from the gastric contents.

Another disease of the stomach in which the question of the source of infection becomes of importance is phlegmonous gastritis. I am aware that the view is held by some that in this disease the inflammation of the wall of the stomach is a metastasis, the result of infective material brought there by the blood-current from a focus elsewhere in the body.

A study of the cases that has been reported gives, however, a distinct impression that in many of them at least this is not the case, and that the infecting bacteria have found their way into the submucous tissues through a lesion in the gastric mucous membrane.

In a case reported by Kelnyack[14] the onset of the symptoms followed the forcible dilatation of a cicatricial stricture of the lower end of the esophagus.

At autopsy there were found the typical lesions of acute diffuse phlegmonous gastritis. At the esophageal stricture there were several deep fissures in the mucous membrane, one of which led down to an abscess of considerable size between the esophagus and trachea.

The relation of the onset of the symptoms to the operation indicated that the trauma was the cause of the disease.

In another case reported to this Association at its last meeting by Dr. Kinnicutt[15] there was a linear cicatrix on the posterior wall of the stomach, at the lower end of which was a small necrotic area, and which suggested the hypothesis that this was the point of entry for the pyogenic organisms.

Hemmeter[16] has reported a case which complicated a carcinomatous ulcer of the stomach.

In a summary by Leith[17] of reported cases of this disease there were two in which a local point of infection in the stomach was evident. In one case there was a gastric ulcer which perforated into the pancreas and which was complicated with phlegmonous gastritis.

In another there were hemorrhagic erosions which were believed to be the source of infection.

In a case of typical diffuse phlegmonous gastritis occurring in my own service during the past year, and not previously reported, there was found at the pylorus a small polyp, the mucous membrane of which was necrotic and the center of which was a mass of pus. This appeared to be the portal of entry for the micro-organisms.

Thus in these six cases there was found an initial lesion in the stomach wall which was thought to have given entry to the pathogenic bacteria. The most reasonable hypothesis seems to be that in this disease the inflammation is set up by bacteria which are in the gastric contents, and which find their way to the submucous coat through some lesion of the mucous membrane.

I am aware that in trying to throw light upon the pathogenesis of mild cases of hectic fever that do not come to autopsy one is leaving the realm of scientific certainty and drifting into that of hypothesis; but a study of the group of cases that have just been detailed has given the impression that septic poisoning through lesions of the

stomach and duodenum is of more frequent occurrence and greater clinical importance than is generally believed, and that the presence of moderate grades of hectic fever may be of some use in the difficult differential diagnosis between functional and organic disease of these organs.

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DISCUSSION.

Dr. Cabot: I would like to ask Dr. James whether there was any leucocytosis in these cases of ulcer with fever?

Dr. Meltzer: It seems to me that the cases Dr. James has mentioned permit another interpretation. If I understood him correctly, his view is that in these cases of atypical septicemic character the gastric or duodenal ulcers have been the whole source of infection. A single entrance of bacteria into the circulation will probably not yet cause septicemia; the normal bactericidal powers of the blood will overcome a single invasion. For the maintenance of a permanent infection of septicemia, either of the two conditions have to be present: either the blood lost its normal bactericidal powers, or else there is a source for continual new infection. I will admit that it might happen once in a while that micro-organisms could invade the circulation by the way of even a gastric ulcer. But it seems to me improbable that such an open surface will present the gate for a continual invasion. Open purulent surfaces do not cause septicemia. I am rather inclined to believe that if, in the course of a gastric ulcer with hemorrhages, undernutrition, etc., septicemia appears, it is to be considered only as a terminal infection. Flexner has shown a few years ago that the cause of death in

many chronic diseases is not the disease itself, but a terminal infection. The normal body is full of bacteria which often invade the circulation, but in health they are taken care of by the normal bactericidal powers. These, however, are greatly reduced in serious chronic diseases, and so the invading bacteria are permitted to grow within the blood, hence the septicemia. Whether these bacteria entered through the ulcer or through any other gate is indifferent, as bacteria probably find their way into the circulation, often even through normal mucous membranes.

DR. KINNICUTT: In reference to the remarks just made, I think many of these cases of fever can hardly be regarded as terminal infections, inasmuch as they occur when the patient is in a fair condition. Trace the chronic ulcer, and you frequently have a slight rise of temperature occurring at irregular intervals over a very long period of time. My own experience has been quite in accord with that of Dr. James, and I have long believed and taught that the fever we so frequently observe in ulcer and cancer of the stomach is the result of infection, probably from the gastric lesions. Another observation which I think others will confirm is the occasional occurrence of other symptoms of infection in ulcer or cancer of the stomach. A number of times in the last few years in the cases of ulcer that have come under my observation there has been infection of the parotid gland, sometimes ending in suppuration. In at least one instance with a fatal issue from hemorrhage the only lesion, aside from the abscess of the parotid, discovered at autopsy, was an active gastric ulcer.

DR. JAMES: In answer to Dr. Cabot I can only say that in a few of the cases blood-counts were made, and in a small proportion of those marked leukocytosis was found, but as there was also hemorrhage not much importance was attached to this point.

RECENT RESEARCH WORK ON THE CHEMISTRY OF THE TUBERCLE BACILLUS.

By E. L. TRUDEAU, M.D.,
OF SARANAC LAKE, N. Y.

Allow me to bring briefly to the attention of the Association the results of some researches as yet unpublished which have been carried out in my laboratory this winter by Drs. Levene and Baldwin.

Dr. Phœbus A. Levene, with the assistance of Dr. E. R. Baldwin, who furnished him with the enormous quantity of germs necessary for his chemical analysis, set himself the task of making what may be termed a chemical dissection of the tubercle bacillus. Much work on the chemistry of the tubercle bacillus has been done already by Behring, Hammerschlag, Hoffman, de Schweinitz, and Ruppel. As a result of Dr. Levene's work, I show you in these flasks the various substances which he has thus far been able to isolate from the dried and crushed germs. The first flask contains a coloring-matter, an alcoholic extract of the washed, dried, and powdered bacilli. That this coloring-matter is peculiar to the tubercle bacillus seems to be indicated by the fact that a few drops of it added to a glass of water give the same opalescent, yellowish-green hue which is noticed in cultures growing on transparent liquid media.

He also separated a peculiar fat or wax-like substance which I now show you, and which forms 30 per cent. of the body substance of the bacillus. When the various component parts of the bacillus are stained this is the only one which holds the stain in the presence of acids. It does not seem to be a toxin which causes the fever, since Dr. Baldwin demonstrated that animals inoculated with bacilli freed from fat react to tuberculin in the usual way.

Dr. Levene also separated three nucleoproteids which have different coagulation points. From these he obtained a nucleic acid, which I now show you, and which he found to contain more phosphorus than nucleic acid derived from other animal and vegetable substances that he tested. The nucleoproteids of the tubercle bacillus are probably the toxic agent, or at least one of the toxic substances, contained in the bacilli. This was demonstrated in a set of experiments I will refer to again, where the toxicity of tuberculin was shown to be destroyed by those ferments which are known to be especially active in splitting up nucleoproteids.

Beside these substances Dr. Levene found a glycogen or a glycogen-like substance which is contained in this small flask. This is the first time, to my knowledge, that this substance has been demonstrated in the tubercle bacillus, though the presence of carbohydrates has been suspected as a necessary source of energy in bacteria.

He also studied the chemical differences in cultures grown on different media, in virulent and less virulent cultures, to determine the relation the chemical composition of bacteria might bear to their virulence. Comparative studies were made of bacilli grown on ordinary bouillon and on a synthetic medium described by Proskauer and Beck, containing chiefly phosphates, mannite, and glycerin. Results show that more fat and a larger amount of proteid and free nucleic acid could be obtained from bouillon than from mannite cultures, and it would appear that toxic properties of bacillus are probably related to the nucleic acid and its combinations which they contain.

Another interesting set of experiments by Dr. Levene and Dr. Baldwin proved that the toxins of tetanus, diphtheria, and tuberculosis are all destroyed by digestion with trypsin, and the first two by pepsin and papain also. When thus treated a dose ten times as large as a usually fatal dose is harmless. Tuberculin could not be destroyed entirely by peptic digestion, and it is probable from this fact that it is a nucleoproteid, this group of proteids being more resistant to pepsin.

SOME TROPHONEUROSES AND THEIR RELATION TO VASCULAR DISEASE OF THE EXTREMITIES.

By B. SACHS, M.D.,
OF NEW YORK.

In an article on erythromelalgia,[1] published a few years ago in conjunction with Dr. A. Wiener, it was shown that marked changes had taken place in the bloodvessels of the affected extremity. The amputation of the leg above the knee furnished the opportunity for a careful examination of the nerves and bloodvessels of the diseased part, and it was found that these marked changes in the bloodvessels occurred not only in the immediate vicinity of the most affected region, but were equally pronounced in the bloodvessels at some distance from the site of the disease. From this the conclusion was drawn that in some instances the symptom-group known as erythromelalgia may be due to disease of the arteries rather than to disease of the peripheral or central nervous system. The anatomical findings in this case were a surprise to us, but have encouraged us to study in somewhat greater detail the relation of vascular disease to trophoneuroses of various types. These special affections have in the minds of all of us been associated far more with disease of the nervous system than with disease of the arteries or the veins, and it is probably due to the surprise occasioned by the findings reported by Dr. Wiener and myself that our former publication met with some criticism.

It has been claimed by several writers[2]—among others by Cassirer,[3] in his recent able monograph on vasomotor and trophoneuroses—that the case of erythromelalgia in which these marked

[1] Deutsch Zeitschrift für Nervenheilkunde, 1899, Bd. xv. p. 286.
[2] G. Schrötter. Nothnagel's specielle Pathologie u. Therapie, vol. xv., Theil iii. p. 397.
[3] Cassirer. Die Vasomolorisch-trophischen Neurosen. Berlin, S. Karger, 1901.

changes were found did not conform to the type of the disease, but could be interpreted as a form of obliterating endarteritis. A careful review of the entire course of this case of erythromelalgia shows that it conforms to the type as developed by Weir Mitchell. The patient was a man, aged thirty-six years, a Russian, who had had vague rheumatic pains for some years, which he connected in part with the necessity of working ten or twelve hours at a time at a sewing-machine. At first there were spasmodic attacks, redness and swelling of the left foot, particularly noticeable when the leg was hanging down; later on the "red neuralgia" became persistent. For a period of over six months there was not a single symptom except those that we are accustomed to find in this disease. There was lively pulsation of the arteries, and the color of the foot changed from a bright red to a violaceous tint. The only symptom in the case which was a little unusual, and which Weir Mitchell[1] did not include in the symptomatology of the disease, was the gradual development of a large ulcer on the dorsum of the foot, which grew worse and worse, and, finally, in addition to the pain, necessitated the amputation of the leg. But other writers, including Elsner,[2] have reported cases of undoubted erythromelalgia associated with gangrene, and even Cassirer has to allow that such marked trophic disturbance may occur in this disease.

German authors in particular, who took up this subject a few years ago, have insisted on *à priori* grounds that erythromelalgia must necessarily be due to disease of the trophic nerves, and were of the opinion that it would prove to be a disease of the posterior gray matter of the spinal cord. No evidence of this has been furnished, and the only complete autopsy in a case of erythromelalgia[3] was in one complicated by tabes dorsalis; in view of this it remains doubtful still whether the changes in the lower lumbar and upper sacral roots in this case can be held responsible for the trophic changes in the extremity. Weir Mitchell, in one of his latest studies, allows for the possibility of a central origin of the disease, but pleads much more strongly in favor of a nerve-end neuritis as a direct cause of the symptoms of erythromelalgia; and in a paper

[1] Clinical Lessons on Nervous Diseases, Philadelphia, 1897, p. 180.
[2] New York Medical Record, 1897, vol. li. p. 172.
[3] Reported by Auerbach, Deutsch Zeitschrift für Nervenheilkunde, Bd. xi. p. 143.

published in conjunction with Spiller it is shown that there were slight vascular changes in addition to the evidences of a terminal neuritis.

I have no intention, however, at the present moment of proving or disproving the diagnosis of erythromelalgia in the case previously reported. Whatever name one chooses to give to the series of symptoms met with in many of these cases, it is very certain that erythromelalgia, Raynaud's disease, acroparesthesia, and even scleroderma often merge into each other or are associated with one another; and whether these various types be due to nerve disease or not, the fact stands out clearly for the present that marked forms of arteriosclerosis and phlebosclerosis occur in association with these so-called trophoneurotic diseases.[1] It is the special object of this paper to report a number of cases of vasomotor and trophoneurotic disturbances in which the condition of the nerves, arteries, and veins of the affected extremity has been carefully studied. Incidentally we shall be able to refer to the fact that the lesser stages of the disease are in all probability responsible for many cases of vague "rheumatoid" pains in the arms and legs, for paresthesia in cases of diabetes, and for conditions resembling those of local syncope in pronounced cases of arteriosclerosis. Medical men have for years given most careful consideration to endarteritis as it occurs in the brain, but have troubled themselves far less about the same condition as affecting the peripheral parts of the body, and have not held these arterial changes responsible for symptoms which might better be attributed to them than to the influence of trophic nerve fibers, the distribution and function of which are still but vaguely known. A closer study of peripheral arterial changes is bound to follow. Spiller has referred to them in an article published in the *Journal of Experimental Medicine*, on a report of a case of dermatitis vesiculo bullosa, and has considered the relation of vascular nerve changes to spontaneous gangrene and Raynaud's disease, and more recently Wulff,[2] of Berlin, has reported similar disease of the bloodvessels causing spontaneous gangrene in a youthful subject. Some will

[1] Somewhat similar views were expressed in an article just brought to our notice: "On Symmetrical Gangrene," by A. Sturmdorf, Medical Record, August 1, 1891.

[2] Ueber Spontan Gangraen bei jugendlichen Individuer. Berlin Surgical Society, December 10, 1900, reported in Deutsch med. Wochenschrift, 1901, No. 9, p. 68.

contend that however great the arterial or vascular changes may be, they are secondary to some mysterious trophic influence. There is, of course, much to be said in favor of this view.

Lewaschew's[1] experiments on animals have shown that five months after irritating the sciatic nerve of an animal distinct changes were noted in the bloodvessels of the part experimented upon; that there was a constriction of the vessels due to the marked changes, first in the adventitia and muscular coat, and later on in the intima of the smaller bloodvessels. Fränkel[2] found changes in the bloodvessels three or four weeks after section of the sciatic nerve. It was his opinion that the nerve lesion produces a condition of chronic irritation; that this in turn was responsible for a spasm of the arteries, resulting in an hypertrophy of the walls of the bloodvessels. Among the most recent writers on the subject is Lapinsky,[3] who has shown conclusively that section of the vasomotor nerves produces a change in the walls of the bloodvessels. He operated on fourteen rabbits, removing various sympathetic ganglia, and also performed resection and ligation of the cervical sympathetic. Following upon these operations he observed a dilatation of the bloodvessels, more marked pulsation, and increased blood-pressure. The animals were kept for varying periods from between ten to ninety days. In seven out of the fourteen cases there were marked changes in the larger bloodvessels, consisting of the thickening of the muscular coat and of the elastic membrane. The changes in the smaller bloodvessels and in the capillaries were still more marked. The muscular coat was either atrophic or had disappeared entirely. The intima was thickened and proliferated, the lumen of the bloodvessels being frequently closed. If the animals were killed before six weeks had elapsed since the operation the degeneration of the walls was not so evident. The nature of the lesion itself and of the sympathetic did not seem to be of any special importance, and it mattered little whether or not the ganglia had been removed at the time the sympathetic was experimented upon. Lapinsky has also done excellent work in showing the dependence of vasomotor changes upon neuritis. He was able to furnish accurate anatomical evidence of a proliferation

[1] Virchow's Archiv, vol. xcii, p. 152.
[2] Centralblatt f. allg. Pathologie u. Path. Anatomie, 1898, i., quoted by Cassirer.
[3] Deutsch Zeitschrift f. Nervenheilkunde, vol. xvi. p. 240.

of the intima with obliteration of the lumen, and of hemorrhages into the surrounding tissue following upon an experimental neuritis. But granted that the sympathetic and the peripheral nerves exercise an important influence upon the bloodvessels, the question arises whether disease of the bloodvessels may not occur independently of nerve lesions or possibly coincident with them. Such coincidence would not be unnatural if we reflect that there are several organic and inorganic poisons, such as syphilis and alcohol, which exhibit their deleterious effects upon the bloodvessels as well as upon the nerves.

While Lapinsky is inclined to attach greater importance to reflex neurotic influences, Thoma has established the doctrine that the degeneration of the bloodvessels is largely due to simple mechanical conditions, and that the retardation in the rapidity of circulation and the variations in intravascular pressure are primarily responsible for the changes in the walls of the bloodvessels. Cassirer, who has tried in an impartial way to review the entire literature of the influence of the trophic nerves upon the disease of the bloodvessels, is only able to state, as a final conclusion, that "there is at least every reason to consider the condition of the vasomotor symptom in cases of disease of the bloodvessels, particularly of the smaller ones." If this be the result of years of controversy it will be more fruitful to quit the field of speculative physiology and pathology, and to record for the present, in sober fashion, the wide-spread changes in the vascular system of patients affected with various forms of so-called trophoneuroses. To this end a few histories and anatomic studies will be briefly reported:

Case I.—W. S., aged twenty-seven years, born in Russia. Seen for the first time in January, 1898. At that time he complained of a peculiar numbness and tingling sensation in his feet. These would occur at various times during the day, and were followed by severe pain and a distinct bluish discoloration of the feet. The patient thinks that for four years before this first examination he had suffered in a similar way. He was employed in a silk factory, and was compelled to stand on his feet all day. The pain was paroxysmal, sometimes lasting only a few moments; at other times it would continue for several hours. He suffered more during the winter than during the summer months, although never entirely free from pain. Holding his occupation responsible for his symptoms, he changed the character of his work and was busy at a sewing-machine. After working in this way only a short time, and sometimes treading the machine with his bare feet,

occasional pain set in in both feet, and he soon noticed that the right one assumed a dark purplish color. The paroxysmal attacks of pain became more and more frequent, the individual attacks lasting longer and longer, until the pain became practically continuous. There is no history of syphilis in this case. The urine was normal, free from sugar or any foreign matter. He had been a heavy drinker for some time, never becoming intoxicated, but rather proud of the fact that he could consume large quantities. The toes of the right foot at the time of the first examination had assumed a dark purplish color. When pricked with a pin the blood that exuded from the toes was almost black. The veins over the arch of the foot were prominent; pulsation could be felt in the arteries at the ankle-joint, but not very distinctly. The feet were not sensitive to pressure, even at the time of greatest pain. The left foot was similar in every way, though all the phenomena were somewhat less marked. No sensory disturbances could be detected in either foot in the interval between the attacks. The electrical condition of the nerves and muscles was practically normal. Various therapeutic measures were employed, but without avail. The patient was evidently discouraged, and disappeared from observation.

He returned a year and a half later with the history that he had gone to his home in Warsaw, Russia, and had placed himself there under the care of a physician. While there gangrene appeared, and one toe after the other of the right foot had to be removed during a period of two months. Soon the toes of the left foot began to give the same trouble, and the big toe of this foot was also removed on account of the gangrene. Later on the little toe was removed. The other toes were extremely cyanotic, but were not amputated. The patient felt better and decided to return to New York. When examined after his return the following condition was noted: The right foot presented a reddish-purplish appearance, with veins still prominent and arteries with distinct but weak pulsation. The left foot was of much darker appearance; the only three toes which had not been amputated were extremely cyanotic. At this time the patient was working in a cigar factory. He was under observation just one month, when severe pain and gangrene occurred on the inner and plantar surface of the left foot. On account of the pain and marked cyanotic appearance of the foot, amputation had to be resorted to, and this was done by Dr. Lilienthal, the patient making an uneventful recovery. Previous to the amputation of the foot the patient began to complain of pain and numbness in the index and middle fingers of the right hand. These fingers would get perfectly white, and were practically corpse fingers, in marked contrast to the deep cyanotic color of the other fingers and rest of the hand. The pulse at the wrist did not alter its character appreciably during the entire attack. It was of great interest to us, however, that at this time a marked phlebitic swelling occurred just below the elbow. This gradually disappeared under proper treatment.

The paroxysmal attacks of pain, the recurrent forms of local syncope and asphyxia, followed by symmetrical gangrene, the absence

of marked sensory changes and of a reaction of a degeneration in the nerves and muscles of the affected parts, made the diagnosis of Raynaud's disease certain enough. But even if there were to be a difference of opinion as to the exact labelling of this special case the marked arteriosclerosis and phlebosclerosis were of special interest. On carefully examining the removed tissue we could not find a single artery or vein, large or small, that was not diseased. Slight degenerative changes were found in some of the nerve fibers. Excessive alcoholic indulgence and the peculiar occupation of the individual must be considered the chief etiologic factors. With alcohol as a predisposing cause of vascular disease, the constant use of the extremities may be considered to be the additional exciting cause. Moreover, as soon as the patient changed his occupation and became a cigarmaker, necessitating the more active employment of the hands and fingers, the disease became evident in the upper extremity. Exposure to cold may also have played a rôle, and, in view of the diseased condition of the bloodvessels, reactive circulation could not be easily established in parts that were improperly nourished. The obliterating endarteritis in this case was evidently not of recent date. An examination of the specimens showed some of the vessels almost completely obliterated by dense sclerotic tissue, while all possible and advanced stages of an obliterating endarteritis could be made out. The presence of phlebitic swelling in the right forearm coincident with the first symptom of the Raynaud type in this same extremity would also go to prove the intimate dependence of the latter upon the former. The patient, on close questioning, also stated that he had frequently had these lumps in the lower extremity before the later symptoms had been carefully noted. It will not be necessary to claim that Raynaud's disease is always due to vascular changes, though Barlow, Dehio, and even Raynaud himself have reported such changes in subjects of this disease. Allowing for the marked trophic and vasomotor influences, the case just reported seems to us to furnish good evidence of the intimate relation between the vascular changes and the grave disturbances in the nutrition of the peripheral parts.

CASE II.—S. L., a tailor, aged thirty-one years; married seven years; family history negative as far as any neurotic taint is concerned. Smokes a pipe and drinks beer very freely. No history of any venereal trouble. Has

worked at a sewing-machine for four years, but gave up this occupation three years ago. Has never suffered any exposure to cold. Four years before the first examination he claims that he suffered with occasional burning pains along the inner border of the left foot and drawing pains of the left calf. These attacks were infrequent at first, and lasted about half a day. He noticed that at times a red patch would appear over the inner border of this same foot, without any distinct pain in walking. Two and a half years ago he began to suffer from redness and swelling in the big toe of the left foot, which was accompanied by a marked burning sensation. The pain, the redness, and the swelling were constant, but were made distinctly worse on walking. The trouble was supposed to be rheumatic, and the treatment was in accordance with this supposition. This treatment was interrupted by the appearance of an ingrowing nail on this same toe. The nail had to be removed, and a black suppurating slough developed, the gangrenous area spreading toward the end of the toe on the outside. This area was excised and the bone thoroughly scraped. Gangrene, however, continued to spread, so that it became necessary to remove the nail and one phalanx, which was done on January 21, 1899. The patient had been in the hospital three weeks, and as the amputation wound refused to heal the sloughing skin and a piece of the proximal phalanx were removed. During all this time the patient had severe pain, and the other toes of the same foot became reddish-blue, were swollen, and were more or less painful. In May, 1899, the proximal phalanx was removed under chloroform, and the wound bid fair to heal. Later on numerous incisions had to be made for evacuation of the pus. The patient insisted on returning to his work, but ulcers were developed between the base of the second and the third toes on the dorsum of the foot. The blueness, pain, and swelling were growing constantly, and especially severe when the foot was in a dependent position. The heart, lungs, and kidneys were normal. The patient weighed about 141 pounds, and was emaciated in appearance. There was a general atrophy of the left limb from the hip down. This atrophy may partly have been due to disuse, as the patient had not practically used his limb for a period of four and a half months. The deep and superficial reflexes were normal. The left foot, when in a dependent position, becomes cyanotic; when elevated, it gradually grew paler, but remained elevated. The great toe is absent, and the others are swollen, so that the lines over and around the articulation are lost.

The nails are thick, round in shape, and with a tendency to become ingrown. Under the dorsum of the right foot at the head of the first metacarpal bone is a round, circumscribed ulcer, three centimeters in diameter, which involved the entire thickness of the skin. The borders are not undermined, but sharp, and bleed easily when the foot is dependent. At the base of the muscles is a yellow-grayish slough, and does not bleed easily. Around the ulcer the skin has a reddish-blue color, which disappears slowly and returns gradually on pressure. On the dorsum of this foot and base of the second and third mediodorsal phalangeal articulation is another ulcer similar

in every respect to the one just described, only differing in size and shape. The pain became so severe in this case, and the ulcers refusing to heal, various therapeutic measures were tried, and the leg was amputated above the knee-joint by Dr. Gerster. The popliteal artery, vein, and nerve, the anterior and posterior tibial arteries, veins, and nerves, together with the plantar arteries and nerves and various tissues of the foot, were immediately removed and examined.

In this case, also, all the veins and arteries were in a condition which might best be designated as a marked arteriosclerosis and phlebosclerosis. The popliteal nerve was entirely normal. Only in the neighborhood of the ankle-joint were a few degenerated fibers in the anterior and posterior tibials. There was a distinct neuritis of the nerves on the dorsal and plantar portion of the foot. In this case, again, if we were interested in the diagnosis of erythromelalgia, a hue and cry would be certain to be raised; although the swelling, the redness, the pain, the marked hyperesthesia, all increasing when the foot was in a dependent position, would be in agreement with that diagnosis. But we will not insist on it, since the clinical picture was evidently entirely altered through the presence of an ingrowing nail, and possible infection of the foot leading to the ulceration and gangrene. There would be no objection to classifying this special case as a representative of the simple obliterating endarteritis of Friedlander, and to meet all just criticisms it may simply be inferred that the earlier stages of obliterating endarteritis give rise to symptoms which are very similar to those included under the term of erythromelalgia. The occurrence of marked pain in these cases is of some interest. It would be natural to connect this with a terminal neuritis, as Weir Mitchell has done in his classical accounts of erythromelalgia; but one cannot escape the conclusion that the terminal neuritis may at times be secondary to this marked alteration of the bloodvessels, with subsequent malnutrition of all the tissues, including the nerves. In the case just referred to the parent trunks were normal, and changes were found only in the more peripheral portions. When gangrene and ulceration appear the neuritis may be attributed, in part, also to the effects of the infection.

CASE III.—The patient, Mrs. S. I., aged twenty-nine years, was referred to Dr. Winer by Dr. Goldenberg. She was born in Germany; married eight years; inclined to obesity, and presented various gouty manifestations. Short

and thick-set in stature, she easily tires and suffers from palpitation and dyspnea when she attempts to walk rapidly or to climb a flight of stairs. Of the four children born to her, none is living. During first pregnancy she had a bad fall in the seventh month. The child was born at term and died shortly after birth. With the second child labor was difficult; the child was born alive and died on the following day. The third was born at full term and died a few days thereafter in convulsions. The fourth child lived to be six months of age, and then died in an attack of pneumonia. The patient has never had any serious illness and gives no history of syphilis or of any venereal infection, however suspicious the history may be. Her mother died at a very early age of unknown disease. Father is living and well. The parents of the patient have had seven children. Of these seven, five are living and perfectly healthy. In regard to the other two, one died of meningitis, complicating influenza, and the other of pernicious anemia. The patient's husband is living, and has been free from serious illness. In the spring of 1900 the patient's foot began to itch in a very annoying manner, so that she often was compelled to remove her shoes during the day to relieve the itching by scratching. It was especially severe in the neighborhood of the small and middle toes of the right foot and the small and big toes of the left foot. At first there was no pain, but gradually the pain appeared after scratching. After a period of three weeks, following upon the mechanical irritation produced by scratching, excoriated areas appeared over the big and second toes of the left foot. The ordinary treatment by dry powders was of no avail; the excoriations gradually developed into ulcers, and the patient requested treatment at the Vanderbilt clinic. She was put under thorough anti-syphilitic treatment, which had no effect on the healing of these ulcers. The pain became continuous, was burning in character, and so severe that she was unable to obtain a night's sleep. After further treatment by Dr. Goldenberg, consisting of ichthyol ointment and cold dressings, which also proved unavailing, the patient was sent to Mount Sinai Hospital, where, after remaining at rest for a few weeks, the ulcers gradually healed; but as soon as she was up and about again the same condition returned. It was then decided to amputate the big and second toes upon which the ulcers existed. Considerable relief followed upon this, and the patient has been up and about for six months. The urine was examined several times and found to be normal; only once a very slight trace of sugar was made out, to which, however, no importance could be attached. No distinct sensory disturbances were ever detected. The deep and superficial reflexes were always normal. Distinct and good pulsation was present in this foot. The toes just before amputation were very much swollen and of a reddish-purple appearance. The base of the ulcers was covered by a thin, grayish, purulent-looking mass. The edges were not undermined or thickened.

A microscopic examination of the tissues taken from the amputated toes shows an obliterating endocarditis in its earlier stages and also a nerve endar-

teritis. No normal nerve fibers could be made out in the many specimens that were examined. The tissues were infiltrated with the round cells and showed an active inflammatory condition. This case demonstrates the earlier presence of vascular disease in association with nerve neuritis and with trophic disturbances. It is not unimportant to note the early and persistent itching. The scratching, the mechanical irritation, as well as the infection, evidently led to the development of ulcers in parts embarrassed by a defective circulation, due to diseased bloodvessels.

In the three cases just reported somewhat in detail, the relation to the trophic disturbances and the vascular disease seems to be evident enough; but since our attention has been directed to the observation of the bloodvessels in the extremities other and lesser conditions have been met with which may properly be attributed to lesser and possibly recoverable affections of the peripheral bloodvessels. Some time ago we had under observation a lady, aged fifty-five years, who had been treated for an attack of hemiplegia due to embolism. The patient had a marked general arteriosclerosis in addition to the valvular lesion without any renal complications. She has recovered from the hemiplegia, and is now able to get about without assistance. Her general health is good, but she is troubled from time to time by spasmodic attacks of severe pain in the fingers of the right hand, followed by numbness and pallor of these fingers. The attack generally does not last more than a few hours. During several such attacks I was called to see her, and found that the fingers were absolutely numb and resembled in every respect the corpse fingers of Raynaud's disease. Each one of these attacks has been promptly relieved by the administration of hot baths, vigorous massage, and small doses of iodids. The attacks could justly be likened to those of Raynaud's disease, but the matter is referred to here merely to show the probable dependence of such symptoms upon arteriosclerosis of the peripheral vessels. It is a matter for surprise that such attacks are not more frequently referred to in association with cardiac arterial disease in the senile period.

In another elderly lady, aged sixty years, suffering from severe diabetes and treated in conjunction with Dr. Janeway, the most distressing symptoms were frequent burning sensations, numbness, and occasionally a cold feeling in the lower extremity. We might have been satisfied merely to record these as ordinary rheumatoid pains, for there was also a gouty rheumatic element in this case; but,

bearing in mind the possible disease of the peripheral arteries, we watched carefully the pulsations of the dorsal artery of the foot, and often found its beat feeble. Relief in this case was only to be had from active massage and the application of intense heat. There can be little doubt that such symptoms as these are due to interference with the peripheral circulation. If we bear in mind the frequency of gangrene in diabetes the occurrence of such symptoms as we have just described, denoting a lesser degree of vascular disease, becomes a matter of more than passing interest.

It would, indeed, be well to pay greater attention to the arteries of the lower extremities, for not only are such rare types of disease as intermittent claudication known to be associated with arteriosclerosis in the lower extremities, but Thoma's interesting researches have shown quite conclusively that many of the vague rheumatoid affections may be considered to be due to an angiosclerosis.

Whatever theory we may hold with regard to the influence of trophic and vasomotor fibers upon disease of the bloodvessels, the experience here reported seems to argue in favor of an intimate relation between the disease of the peripheral bloodvessels and many of the trophoneuroses, and whether such disease be primary or secondary must be left to further investigation.

DISCUSSION.

DR. JANEWAY: I was very glad to hear Dr. Sachs go into this subject in detail. I saw a case last year affected in the reverse order to the one he described—that is, the patient having the trouble with his hands was advised to take exercise on the bicycle, and soon the disease affected his feet. I could recognize in that case that the arterial pulsations in the fingers and in the feet were markedly reduced. When I first heard of the case I was told that it was a gangrene of the extremities, and I at once asked for a specimen of the urine, expecting to find diabetes. I found, however, some albumin and considerable amount of casts. The latter persisted for a time and then cleared up, and I was uncertain whether it was a part of the disease or due to very large doses of aconitin given for a long time to relieve pain. This case had at first been called erythromelalgia, and the name was shifted to Raynaud's disease, as happens not infrequently. My belief is that in cases like this the defective vascular supply through arterial change is primary; in one case similar leading to amputation from extension. This was proven.

DR. OSLER: With reference to the important point brought out by Dr. Sachs bearing on the relation of pain in the extremities to arterial disease, I think this is noted more particularly in diabetes. I have had the opportunity to see two brothers with this condition of the toes, and both having within two weeks of each other gangrene of the feet. In a certain number of cases in elderly people, with numbness, tingling, and pains in the legs, I think the association with arteriosclerosis and phlebosclerosis has been well made out.

DR. PUTNAM: It is interesting to note that although the various sorts of cases described by Dr. Sachs are more or less closely related and united by intermediate forms, yet as such they preserve, each one, a striking independence of type and run remarkably true.

DR. SACHS: In order not to be misunderstood, I would say that I do not wish to claim that these cases are all due to diseases of the bloodvessels, but that in many instances the trouble is due to disease in the vessels rather than in the nerves. The only other point I want to mention is that in the past few years I have been examining the arteria dorsalis pedis as well as the radial arteries, and would suggest that it is well worth while paying closer attention to the arteries of the lower extremities.

THE HEREDITY OF APPENDICITIS.

By F. FORCHHEIMER, M.D.,
OF CINCINNATI.

THE heredity of appendicitis has been referred to in a general way for some time, but it is only within the last five or six years that our especial attention has been called to the occurrence of appendicitis as the result of heredity or family influences. Talamon explains the fact of this factor having been overlooked by the statement that the clinical forms and the methods of treatment have been the principal points discussed, to the neglect of etiology. However this may be, there being not a small number of articles on etiology of appendicitis that have appeared before 1895, the fact remains that heredity in appendicitis is rarely referred to in the literature published before this date.

Among the French the following have reported hereditary appendicitis: Brun, appendicitis in a man whose father had died of perforating appendicitis; MM. Routier, Jalaguier, Quenu, and Berger relate instances of the existence of appendicitis in members of the same family; M. Tuffier reports three brothers with appendicitis; Dr. Haussmann, three members of the same family; Roux, of Lausanne, in 300 personal observations shows the existence of heredity in an astonishingly large number of cases—40 per cent.; and, finally, Talamon, from whom these references are taken, reports two instances, one in father and daughter, the other in two brothers.

Among the English authors we find Atkinson (1895) reporting father, two sons, and a daughter; Taylor (1896), two brothers and a sister; and Treves (1897) states that "Heredity is not easy to demonstrate in a disease so common as that under consideration, but it is impossible not to be struck with the fact that perityphlitis runs often in families." He has seen it in a family "among whose members were five subjects of perityphlitis."

Among the Germans, Sahli has found five members of a family with appendicitis; and Pribrâm (1899) reports two families—in one, three brothers with mild appendicitis, in a cousin fatal gangrenous appendicitis, and in a near relative of the latter a severe case of ileocecal invagination; in the other family, severe appendicitis in a girl, and a fatal case in her cousin.

Deaver reports operating upon three members of the same family; but I know of no publication in American literature in which special reference is made to the heredity of appendicitis.

For the last twelve years my attention has been called to the occurrence of appendicitis in families, and the results of these observations form the basis of this paper. All the cases have been observed in private practice, and, with the exception of four cases, they have all been under my care during one or the other attack of appendicitis. Two cases occurred before the term appendicitis was introduced to us: the one in 1869 and the other in 1883. Special reference will have to be made to the former. In the latter repeated attacks showed that this "uncouth" term, as Treves calls it, could be applied to them.

Beside these hereditary cases tabulated, one other family has come under my observation; two of my medical friends have narrated their observations to me, but I hope to be able to verify the heredity of the disease without taking these into consideration.

I have three tables to present for your consideration, the first one representing four generations, with the following family history: Mother and father emigrated to this country from Germany early in life, the father being a very successful merchant, and dying at the age of seventy-three years; the mother, an intelligent, good housewife, dying at seventy, of diabetes mellitus. There is no history of appendicitis in this generation or of anything that can be considered such. There were born to this couple five children, two males and three females. Of the two sons one was a physician (No. 5), who died at forty-two years, of myocardial insufficiency; the other (No. 3) is a merchant, fifty-seven years of age, who also has a valvular cardiac lesion. Of the three daughters, one (No. 6) died of diabetes mellitus, at forty-five years of age; the oldest one (No. 4), at fifty-three years of age, has a combined cardiac lesion, insufficiency of the aortic and mitral valves. The remain-

ing daughter, outside of obesity, is well, at forty-four years of age. They all have migraine. All three married merchants who have not been successful. All the members of this generation have suffered from nervous dyspepsia; all more or less neurotic, whether as the result of race or external causes I am not prepared to say. Diabetes mellitus, obesity, and valvular lesions of the heart, the latter especially in connection with arteriosclerotic changes (present in Nos. 3 and 4), would lead us to think of those conditions summed up under the head of gout. In none of the members of this generation has there ever been any condition even simulating appendicitis, yet the fact must not be lost sight of that in all of them there was some trouble with the gastrointestinal tract, notably irregularity of the bowels. In the third generation we find fifteen members, with five cases of appendicitis (Nos. 9, 13, 14, 17, 18), two of whom are males and three females. Of this number, three (Nos. 9, 13, 17) were under my care in one or another attack; the other two (Nos. 14, 18) were reported to me. It will be observed that the five cases are distributed in such manner that two brothers and sisters are affected in two instances; and in the third it is a cousin, the children of two daughters and one son (Nos. 3, 4, 6) of the second generation with diabetes mellitus and cardiac troubles. The history of the attacks, in brief, is as follows:

No. 9, a boy now fourteen years old, always more or less constipated, had an attack of intestinal obstruction as an infant, at nine years, and at eleven he had attacks of mild appendicitis ending in resolution, and has been well since.

No. 13, at the age of ten years had an ordinary attack of appendicitis ending in resolution (Treves), following an extraordinary indiscretion in diet, from which she recovered just in time to be saved from operative interference. She had attacks at eleven, twelve, thirteen, and fourteen years, usually in the spring of the year. She is now twenty-five years of age, has not had an attack for eleven years, and is perfectly well.

No. 13 had the same kind of an attack at eighteen years of age, from which she did not recover as to general health and localized swelling, so that she was operated upon seven months after the attack, and is now twenty-three years of age, and perfectly well.

Of the two children of No. 6, the male had his first attack of

ordinary appendicitis at twelve years of age. Attacks occurred during his twelfth, thirteenth, and fourteenth year. In the last year he was operated upon. He is now twenty-two years of age and well.

The female had appendicitis at twelve to fourteen and sixteen years of age. She is now twenty-three, married, the mother of a child, and well. Curiously enough, the one operated upon remains constipated, and the other has no difficulty in this direction.

It is interesting to note here that two cousins (children of the father's brother) have had recurring appendicitis.

In the fourth generation there are as yet only three members, too young and not sufficiently numerous to play any great rôle so far as appendicitis is concerned.

To summarize: We have here a family of twenty-five members, five of whom have had appendicitis, of which four were relapsing and one was operated upon after the first attack. Of the four with relapsing form only one has been operated upon; the other three have been free from relapses three, seven, and eleven years respectively. There was no mortality.

Strictly speaking, the term heredity must be confined to such conditions as are transmitted from one generation to another, in which sense of the word there is no heredity in this family; but that condition which is called "familiär" by the Germans, and which has been translated into English by some authors as familiar. This condition is the one that Treves refers to when he says "that the association of this affection in families is not so often that of parent and child as of brother and sister." This has seemed to me to be the most common coincidence.

Table II. presents a family composed of fifty-two members, in three generations. All the members in the first and second generation have lived in affluence, and their life has been spent in managing their estates, combined with such employment as was congenial to them. The ancestry of both Nos. 1 and 2 is American —*i. e.*, as much as any can be American, the ancestry on both sides coming from Virginia for four generations and probably from England before this time.

No. 1 died of the consequences of an enlarged prostate gland, at seventy-four years of age, his father having died of colic at seventy-

six; his wife died of senile marasmus; she had all her lifetime been subject to constipation.

No. 3, the oldest son, an author, died of a malignant tumor arising from between the bladder and the rectum.

No. 4, an active man of affairs, had Bright's disease, arteriosclerosis, and died in his first attack of angina pectoris, at fifty-eight years

No. 5, male, a writer on a subject upon which he is considered authority, has arteriosclerosis, is a neurasthenic and alcoholic, and is fifty-nine years of age.

No. 6, male, a graduate in medicine, has arteriosclerosis, is neurasthenic, alcoholic, and has had two attacks of mild appendicitis, one at fifty-three years and another recently (at fifty-nine years).

No. 7, a male, aged fifty-seven years, has managed the estate of his father until comparatively recently; he is extremely emotional, and has had at least two severe attacks of neurasthenia.

No. 8, male, aged forty-nine years, a graduate in medicine, neurasthenic, had an attack of appendicitis, with suppuration, when eighteen years of age. The abscess was opened into the bowel, as the result of an examination by Simon's method, the introduction of the hand and as much of the arm as possible into the rectum. He has since had two ischiorectal abscesses; he has vascular disease and is always constipated.

No. 9, male, aged forty-seven years, has had a severe attack of melancholia; is always constipated, and has had one mild attack of appendicitis at thirty-nine years of age.

No. 10, male, aged forty-five years; is also extremely neurotic and constipated.

No. 11, a male, an imbecile, died at thirty years, of measles.

In this generation we find nine members, all males, characterized by the two extremes of intellectuality, the first six of more than average capabilities, the last three falling away very quickly from this characteristic until the last one is reached, who is an imbecile. All the members of this family are affected by some neuropathic taint, beside which they are a "bilious" family—with all that this includes—they can be considered gouty, in the clinical sense of the word. Four of them had arteriosclerosis and one had a

malignant tumor developing near the lower end of the gastrointestinal tract. Finally, we have two members who have had appendicitis.

In the third generation we have twenty-nine members, with the following histories:

No. 12, a male, and No. 13, a female, present nothing abnormal.

No. 14, a man of good business qualifications, absolutely free from nervousness of any sort.

No. 15, female, now thirty-one years of age, has had three attacks of mild appendicitis, at twenty-two to twenty-three and twenty-four years of age; she always has been constipated.

No. 16, a female, died in her first attack of appendicitis, at fifteen years of age.

No. 17, a female, died of typhoid fever, at twenty years of age.

No. 18, a male, not neurotic, but bilious, is thirty-two years of age.

No. 19, a male, aged twenty-six years.

No. 20, a male, neurotic and alcoholic.

No. 21, a female child, died at age of four years, of measles.

No. 22, a female, aged thirty-four years, has had two attacks of mild appendicitis, at eighteen and twenty years of age.

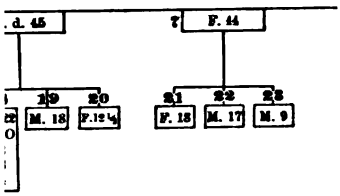
No. 23, a male, aged thirty-two years, is a paranoiac, confined in an asylum.

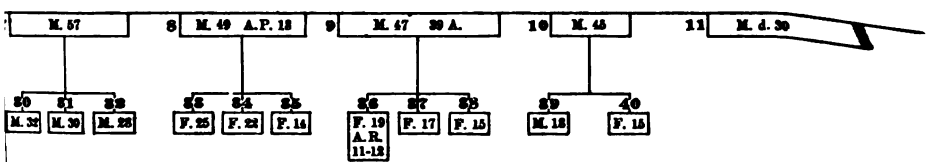
Of the next group, Nos. 24 to 29, I can only report that they are not robust children, and that No. 26, a female, has had three attacks of appendicitis, at the ages of ten, eleven, and twelve years respectively, from which she seems to have recovered completely; and that No. 28 was successfully operated upon for relapsing appendicitis when twelve years of age.

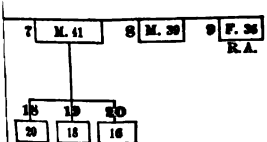
In the next group, Nos. 30, 31, and 32, we find evidences of neuroses, but no appendicitis.

The children of No. 8 are healthy as far as bowel complications are concerned.

Group Nos. 36, 37, and 38 represents three females, all more or less neurotic, the oldest one having had appendicitis twice, once at eleven years of age and again at twelve years, in both instances as the result of gross errors in diet. She is now nineteen years of age, and has not had an attack for seven years.







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in the case of the relapsing form, the ages of the

lains the rest.

The children of No. 10: the girl is most obstinately constipated, the boy is neurotic.

In this generation we have six members who have had appendicitis, with one death; three of these cases occurring in children of two fathers who have had appendicitis, showing thus that appendicitis may be hereditary.

In the fourth generation we have eleven members; Nos. 41, 42, 43, and 44 each have a tendency to bowel trouble, 42 having had, in addition, a dilated stomach.

Group Nos. 49, 50, 51, and 52 are all neurotic, with tendency to constipation and repeated gastric attacks. As far as appendicitis is concerned, this generation presents no cases. This would be the case on the doctrine of chance, as appendicitis is exceedingly rare under five years of age, only five members being older than five years, and among these, according to large statistics, only 10 per cent. ought to have appendicitis (Pribrâm).

In this family the hereditary predisposition to appendicitis comes from the father's side—No. 1. The fatal colic of his father may mean much or nothing, but as I have known all the relatives of the mother's side (No. 2) and their descendants, this conclusion seems inevitable. There have been in all nine cases of appendicitis—17 per cent. of the whole family—of which one was fatal, one suppurative, one mild, and six relapsing.

Table III. shows four generations of a New England family whose medical history differs very much from that of the two families discussed before.

In the first generation we find three members, since it happens that the male member was twice married. Under these circumstances it is not difficult to judge from whom the appendicitis was inherited. The male member of the first generation was a man of splendid physique, of great intellectual power, by profession a lawyer, who had served his country in various capacities, filling the highest offices with distinction; he died at the age of seventy-seven years, of an enlarged prostate gland, having for four years previously suffered from senile heart; his first wife died of pneumonia, at thirty-five years; his second wife is healthy at seventy-four years, even to the degree of having recovered from an influenza pneumonia at seventy-three years of age. In the second genera-

tion there are seven members, the two oldest being the children by the first wife; of these the oldest, a male, aged fifty-four years (No. 3), a man of large enterprises, who claims to have been regular as to his bowels, has had an attack of suppurative appendicitis, at forty-seven years, for which he was operated upon, and is well.

The next oldest (No. 4), a male, a lawyer, died of tuberculosis of the lungs, at forty-six years. He had never had any trouble with his alimentary canal, but was neurotic.

The first child (No. 5) of the second wife died in infancy, of "summer complaint."

No. 6, a male, aged forty-six years, a lawyer, who has even at his present age already outstripped his father as to the number and character of positions held, is a man of most excellent health in every respect.

No. 7, a male, a lawyer, aged forty-one years, whom I do not know, is, I am told, a good specimen in every respect.

No. 8 is thirty-nine years of age, the head of a large school for boys, and healthy.

No. 9, a female, aged thirty-six years, had her first attack of appendicitis—"the ordinary form, ending in resolution"—when she was eighteen years of age; another of the same type at twenty, and a third at twenty-one years. I am informed that she has had no attacks since that time. In addition, she has a tendency to phthisis pulmonalis, which has never developed.

We have, then, in this generation six surviving members, whose general characteristics can be summed up as follows: All people of great physical as well as intellectual development, as far as the males are concerned, with the exception of the one who died of phthisis pulmonalis and had a psychosis due to heredity on the mother's side of the family. Of the males, one has had a severe type of appendicitis, and the female the relapsing form.

In the third generation we find all of the children of No. 3 having had appendicitis.

No. 10, a female, has had two mild attacks, at seventeen and at nineteen years of age, and has been well since.

No. 11, a male, died of typhoid fever at sixteen years, having had a very severe attack of appendicitis at thirteen years of age.

No. 12, a male, aged twenty years, had two mild attacks of appendicitis, at fourteen and fifteen years of age.

No. 13, a female, aged eighteen years, has had three attacks of mild appendicitis, beginning at seventeen years.

No. 14, a male, aged twenty-four years, a confirmed neurasthenic, had an ordinary attack ending in resolution, as a complication of influenza, at twenty-two years of age.

The children of No. 7, whose mother is the sister of the wife of No. 9 in Table II., are splendid specimens in every respect.

The children of No. 8 have never come under my observation, but I am told they are healthy.

We have, then, in this generation five attacked by appendicitis; two of the ordinary form, ending in resolution, and three mild, relapsing cases, all ending in recovery. There is in this family history nothing that presents itself as being predisposing to appendicitis in itself. In the first generation we have one case of tuberculosis, which must be looked upon as a terminal affection to the psychosis; and another member, a female, who has had a predisposition to tuberculosis, which has never developed. All the other members in this as well as the succeeding generation have been absolutely free from any tubercular manifestations even as children; a most remarkable hereditary tendency is apparent, in that all the children of No. 4 have had appendicitis.

In this whole family there have been seven cases of appendicitis out of twenty-two members—33 per cent.—one purulent, two of the ordinary type ending in resolution, and four relapsing cases.

If we take into consideration those factors that may predispose to appendicitis by heredity, the fact naturally obtrudes itself that there may be remote and local causes, or both together. Certainly the local cause or condition is the one of most importance, and here we must look to the appendix itself.

It is a rudimentary organ, and as such has less resistance to disease than one not undergoing involution.

It is rudimentary not only because it has lost its functional value in the human being, but also because it does not retain what little function it possesses as late in life as fully developed organs, as is shown by the disappearance of its Lieberkühn's follicles and its adenoid tissue (Pribrâm).

It is of importance to note that its mucosa is well developed and its submucosa comparatively more developed than in any other part of the intestine. Its muscular coat is especially well developed, notably the inner layer of its circular fibres, but in regard to the functional activity of these layers much diversity of opinion exists. That peristalsis does occur cannot be doubted. It has been seen too often, both during operations and several times after the removal of the appendix. That it is adequate to empty the appendix must be doubtful (Treves), and notably in appendices that have been diseased. The blood-supply is inadequate, and the nerve-supply may be anatomically normal but physiologically under par, as is the case in all muscular rudimentary tissues. In its relation to the cecum there are several conditions that may be affected by hereditary transmission. Gerlach's valve may be disregarded; its existence is denied by Clado, and Laffargue (Tuffert) was only able to find it twice in 200 autopsies.

It has been shown that there is a contraction where the appendix joins the cecum (Hodenpyl, and Ribbert found it in 25 per cent. of all his autopsies); this, according to Ribbert, Woelfler, and others, is to be looked upon as an evidence of involution, and not, in the majority of instances, as the result of pathologic change. This malformation may prevent entrance from the cecum and exit from the appendix; but, under all circumstances, it seems not to be so complete as to prevent the entrance of air from the cecum into the appendix (Williams). Williams states, in addition, that "from its position in a pocket-like cavity it is accessible to pressure from an impacted bowel."

Again, the position and direction of the appendix may be affected by heredity; this is of importance on account of the fact that a distorted appendix is more liable to inflammation than one whose lumen is not affected; and, furthermore, that an appendix may empty itself more readily when assisted by the action of the law of gravity.

The length of the appendix, again, is of importance, varying from 2.5 cm. to 21 cm. (Ribbert) or 30 cm. (Talamon) in length; an hereditarily long appendix would find it more difficult to empty itself than one very short, it having been shown that the longer the appendix the more frequently does appendicitis occur (Hodenpyl).

The same may be said of its lumen; the greater its lumen the

greater the chance for inflammation. There may be a something indefinable which tends to disease in this neighborhood by reducing resistance, as I have seen in one family, in which the father died of an epithelioma of the cecum, his daughter having had relapsing appendicitis and her son an ordinary attack of appendicitis after influenza.

Talamon recites the case of two brothers, one of whom died of appendicitis; in the other the right testicle had not descended until he was fourteen years of age; he had an inguinal hernia, with a large canal, and was attacked with appendicitis at seventeen years. The author suggests that this appendicitis may have been due to a vice of development of the appendix. However this may be, from what has been stated, the conclusion is inevitable that the appendix must be looked upon as a veritable "locus minoris resistentiæ." In a general sense all cases of appendicitis have an hereditary origin in that in all human beings the appendix is a rudimentary organ; but, specifically, the appendix has an inherent amount of resistance which may be easily overcome by remote causes.

First among these must be considered disturbances of the gastro-intestinal tract, all those conditions which lead to catarrhal conditions of the alimentary canal, either with or without mechanical or chemical irritations (foreign bodies, errors of diet, etc.); all those leading to constipation more or less developed (present in about 65 per cent. of all cases of appendicitis) and producing appendicitis either directly by preventing the emptying of the appendix or by causing irritative conditions of the head of the colon which extend to the appendix.

Infectious diseases, tuberculosis, actinomycosis, influenza, acute articular rheumatism, typhoid fever, general infection with pus producers may be considered as rarer remote causes of appendicitis, but only remotely affecting heredity, and some not at all.

There must, furthermore, be some connection between irritative processes the result of the action of chemical bodies that are found in the feces, either as the result of digestive changes or as the result of elimination into the intestine, and appendicitis.

Unfortunately, it is at present impossible to prove this statement by direct chemical examination; but as the result of chronic gastro-intestinal autoinfection, so commonly connected with that clinical

picture called lithemia, or goutiness, gastrointestinal symptoms are the rule. It is difficult to determine whether these are the result of trouble with the nervous system or whether certain nervous conditions are produced by the condition of the gastrointestinal tract; but, in either instance, derangement of the nervous mechanism of the bowel may be properly considered a remote cause of appendicitis.

Lastly, we must take into consideration ethnologic causes. The statement has been made that appendicitis is rare in the negro and absent in Japan. Ashmead ascribes as accounting for this in the Japanese the peculiarities of diet, especially the absence of meat, and states that the small intestine is longer in the Japanese than in the European.

Taking all these factors into consideration, it may be possible to come to some conclusion regarding the production of appendicitis in the families referred to before.

Ethnologic causes can be excluded, although Talamon says appendicitis is especially common in Anglo-Saxons; the first family is not Anglo-Saxon, and the others, while living in this country for a great many generations, are probably not to be considered as pure Anglo-Saxons. In addition, the statement of Talamon must be accepted with considerable doubt as to its correctness.

In the first family we have a train of symptoms going through all the members of the second generation, those of gastrointestinal troubles, associated with symptoms on the part of the nervous system and circulatory apparatus; in the third generation we have appendicitis. The third generation is not old enough to have suffered physically from the general disturbances which they have inherited, except in so far as to have a local manifestation of these in the form of appendicitis, to which they are naturally predisposed.

In the second family it is possible that the father of No. 1 had appendicitis; certainly he had bowel trouble. Both the father (1) and the mother (2) had constipation; all the members of the second generation had some gastrointestinal disturbance. They are liberal in their indulgences, food, and drink; they are mentally active, except the last three members; some of them have had neurasthenia, melancholia, and in every respect they would be looked upon as lithemic, and three members have had appendicitis. In

the third generation constipation is the rule, and in the fourth generation there have been two cases of gastriectasis. It seems here that we must accept some inherent weakness of the bowel, as a whole, a deficiency in development of the muscularis, some defect in nerve function, or, possibly, some inherited form of vicious metabolism plus the inherited condition of the appendix.

In the third family there is nothing of general predisposition except possibly in the female, where tuberculosis might be suspected, the constipation in some of the members of the third generation being explained by the condition of the appendix. Here we are dealing with a local predisposition of which it is impossible to state the precise character.

DISCUSSION.

DR. BLACKADER: I would like to report a case, but I must give it from memory, as I am not prepared to discuss the question. About twenty years ago I saw in a family of eight children, four boys and four girls, a fatal case of appendicitis in one of the boys. Three years later one of the brothers was attacked, and, as the operation was not then so much in vogue, I had difficulty in securing the operation until it was too late—a third case in that family, but too late for safety, although it was done in twenty-four hours of the first apparent symptoms. The mother had an attack of appendicitis during pregnancy, abortion occurred, operation was performed, but she died. I have since learned from the father that in the family of the wife's brother two members had died of appendicitis, which makes a remarkable list of cases in one family. This family was distinctly neurotic, but without any special features that I recall.

DR. JACOBI: I know of half a dozen families in which there have been a certain number of cases of appendicitis. In the family of a friend where there are four children, all of them grown up, there have been two cases of appendicitis operated upon. In the family of a physician in New York City, where there are three children, one has been operated on for appendicitis, one has shown symptoms of the disease, and the mother has appendicitis. In the family of another physician, two girls, of seven and of eleven years, were lately operated upon within two weeks. I could report a number of others, and I have never had the slightest doubt that in certain families there occur a number of cases, no matter what the cause is.

DR. FORCHHEIMER: Since coming to Washington I have been able to find several other instances of the family character of appendicitis. Dr. Shattuck

gave me the history of two families, and I am sure the hereditary appearance of the disease must be a common matter. The trouble is, that medical men have not gone into the subject as thoroughly as the surgeon, although it is a medical matter. It seems to me that the hereditary tendency of appendicitis must be of great importance to the physician especially; it is he who is first called; he is the one who sees the rudimentary attacks, and he is expected to treat them. If the physician takes into consideration the condition underlying the heredity of the disease he can do much to prevent further attacks, possibly to save operations. I have found some statistics which tend to show this hereditary tendency in families to the extent of 40 per cent., a much larger percentage than I have found in my cases.

THE IMPORTANCE OF A RECOGNITION OF THE SIGNIFICANCE OF EARLY TUBERCULOSIS IN ITS RELATION TO TREATMENT.

By E. L. TRUDEAU, M.D.,
OF SARANAC LAKE, N. Y.

It would seem almost unnecessary to emphasize the importance of making an early diagnosis in tuberculosis. To reach a positive conclusion before the disease has caused extensive lesions or seriously impaired the patient's resistance, or before a simple tuberculous deposit in the lungs has become complicated by secondary infection, is obviously a matter of vital importance to the patient. The records of the autopsy-table and the clinical results noted in truly incipient cases where intelligent and radical measures are applied at once bear ample evidence to the curability of the incipient stages of the disease, while the terrible fatality of the malady after it has seriously impaired the general health needs no comment.

The results obtained at sanatoria have demonstrated not only that the disease is curable, but that it is curable in direct proportion to the stage at which the treatment is applied. The published reports of the Adirondack Cottage Sanitarium show conclusively the value of an early diagnosis. During the years 1897, 1898, and 1899, of 113 incipient cases 82, or 72 per cent., were discharged from the institution apparently cured, while of 151 advanced cases only 27, or 17.8 per cent., recovered, and not one of 59 far advanced cases was discharged apparently cured.

No doubt the diagnosis of incipient tuberculosis presents often many difficulties. Our standard as to what constitutes a truly incipient case should constantly be made more rigid. Persistent slight cough, with loss of flesh and strength, a slight afternoon rise of temperature of one-half to three-quarters of a degree, and constant lassitude are symptoms which, even without any appreciable signs

on physical examination, point in many cases to incipient tuberculosis, but which are too often disregarded. Perhaps too much importance is attached to the absence of any abnormal signs in the chest, and the case is not looked upon as being tuberculosis until the stethoscope gives ample evidence of its presence in the lung; and yet we know that often all the rational symptoms of the disease are present long before the lesions can be detected by physical examination; that miliary tubercles in the lung may give no appreciable signs, and that physical examination cannot be expected to detect the onset of tuberculous infection in central portions of the lungs or in the glands and deep tissues and organs of the body. Search for the bacillus should be begun early and persisted in as long as any doubt as to the diagnosis exists. Much time and zeal are wasted in the meaningless task of counting the number of bacilli as a guide to prognosis which would be employed to better advantage for the patient in searching for the bacillus while the symptoms are still obscure. The microscope has been of invaluable aid in the diagnosis of tuberculosis, and when the bacillus is found there is no appeal from its decision, but its absence from the expectoration is not necessarily a conclusive criterion. We should not wait always until the tubercle bacillus is found, for it is of immense advantage to the patient if a conclusion can be reached before it appears in the expectoration, as this does not occur until ulceration of the tubercles has already taken place. Too much stress is laid upon the negative results of the microscopic examination, and much valuable time lost on this account. Repeatedly I see cases, beginning with hemoptysis and some failure of health—even when slight afternoon temperature is present, with or without some physical signs in the chest—where the patient is assured that he has not tuberculosis because one or two examinations of the expectoration have failed to reveal the presence of the bacillus.

In the great majority of cases a consideration of the history of the case and a careful study of the rational signs, with a thorough physical examination of the chest and a microscopic examination of any sputum obtainable, aided by a careful X-ray examination of the patient when required, will enable the physician to make an early diagnosis. If this cannot be done, the tuberculin-test has many times helped me to reach a conclusion, and either to reassure the

patient or to insist on prompt and radical measures of treatment without loss of time. It is not often necessary to use it, but its value lies in the fact that it is most applicable and will demonstrate the presence, and give corroborative evidence as to the absence, of a tuberculous process in the body in just that class of incipient cases where the usual methods of diagnosis fail. It is in the detection of incipient tuberculosis that its best field of usefulness lies. Where any marked degree of fever is present from any cause it is less reliable, as the balance of the heat-regulating centers in such cases is already disturbed, and the injections may cause fluctuations of temperature which may be misleading. In my experience it has proved generally reliable and free from any ill effects, and has many times enabled me to insist on prompt and radical measures of treatment months before a conclusion as to the true nature of the disease could have been reached by the usual methods. Its more general application in place of the waiting policy so generally resorted to will, in skilful hands, warn the patient and the physician of the real danger and save many lives.

A diagnosis of truly incipient tuberculosis would, no doubt, be oftener made if its all-important bearing on the treatment was more fully appreciated. My experience in going over the histories each year of many hundred of consumptives would lead me to believe that the grave responsibility which rests on the physician of detecting the disease in its very earliest stages, and the significance of doing so in relation to successful treatment, are not generally realized. In the great majority of cases valuable time (many months and even years) is allowed to elapse since the first symptoms of ill health appeared before the patient is told the nature of his disease and urged to adopt radical measures for its arrest and cure. Too often he is not told that he has tuberculosis until he can no longer be deceived. His disease is labelled grippe, pleurisy, bronchitis, or malaria; he is informed that the blood came from his throat, until persistence of the symptoms, rapid emaciation, constant cough, hectic fever, and sweats make the true nature of his malady but too apparent, when he is advised to give up his occupation and make a change of climate or seek admission to a sanitarium, only to find that the proposed change is of little avail or that he has applied too late and cannot be taken at an institution.

Many patients who come under my observation far advanced in consumption have been advised months previously that they were not *ill enough* to make a change of climate and surroundings necessary. In spite of every effort, much difficulty is experienced in securing incipient cases for admission to the Adirondack Cottage Sanitarium, and 70 per cent. of applicants give histories which make it evident that some of the symptoms of tuberculosis have been present for from one to three years before they were advised to apply for admission. The examiners for the Massachusetts State Hospital for the Treatment of Tuberculosis refuse about 60 per cent. of all who apply because their disease is too far advanced. About the same proportion is refused in our examinations at Saranac Lake, and of the remaining 40 per cent. admitted not more than one-half are really incipient cases.

Recently a gentleman, a member of this Association, who for years has given his services as examiner in a large city for the Sanitarium, made to me the rather discouraging statement that not a single really incipient case of tuberculosis has ever been referred to him for examination. These facts do not look as if the profession was very generally impressed with the importance of an early recognition of the disease or its significance in relation to treatment.

The real difficulty which often exists in making an early diagnosis, the desire of the patient to remain at home as long as possible, the apparently mild character of his indisposition, and the disinclination of the physician to alarm him, explain in a great measure the waiting policy which is so often adopted. The difficulty of making a diagnosis is not always responsible, however, for many cases show from the first symptoms which are almost unmistakable, such as hemoptysis, enlarged lymph-nodes, dry pleurisy, ischiorectal abscess, or night-sweats, but are allowed to continue for months and sometimes for years without a knowledge of the true nature of their disease or urged to adopt the necessary measures for its arrest and cure.

The increased opportunities for observation enjoyed by physicians in charge of sanatoria have already made very evident to them the significance which the early recognition of the disease bears to its successful treatment. At the Massachusetts State Hospital for the Treatment of Tuberculosis patients are admitted from the list

of those who have passed the necessary examination, not in the order in which they have applied, but according to their physical condition, the most favorable cases for treatment being taken first. Dr. Weicker, at the Berlin Congress, stated that at his sanatorium near Goebersdorf, of the cases which he classes as "in initial state," and which were discharged as cured in 1896-97-98, 97 per cent. were still at work on January 1, 1899, while on the same date, of those who when they entered the sanatorium were classed as "advanced phthisis with destructive process," and discharged during the same years, 77 per cent. were dead.

From my own experience I foresee that, although the open-air method and sanitarium regime have given renewed hope in the treatment of this fatal malady, the results obtained in the many institutions now projected or already built will be disappointing unless the all-important bearing of an early diagnosis in the successful treatment of the disease is more generally realized.

DISCUSSION.

DR. MCPHEDRAN: I wish Dr. Trudeau had specified more particularly in regard to these slight rises in temperature, for I find that a good many physicians are alarmed by an afternoon temperature of 99°, which I consider quite normal. I would like to ask more particularly what Dr. Trudeau means by a fever of 0.5°.

DR. TRUDEAU: I should think a rise to 99 or 99½° in the evening, more-or less persistently, though irregularly, had some meaning, though, of course, such a temperature is not necessarily the result of tuberculosis. I was impressed with this one evening while going through the wards of the Boston City Hospital with Dr. Williams, who had promised to show me a pair of normal lungs under the X-rays. He had selected a boy for the normal specimen, and while he was getting ready I chanced to examine his bedside chart and noticed that a fever of 0.5°, and on two evenings of 1°, was recorded. I told Dr. Williams that if we had that boy at Saranac Lake we would suspect tuberculosis. He took the boy down stairs for examination, and found a shadow in the right lung near the apex. Physical examination disclosed slight dulness and prolonged expiration. We gave the boy tuberculin that night and the next day he showed the usual reaction in a temperature of 103°.

DR. JACOBI: Where does Dr. Trudeau generally take his temperatures?

DR. TRUDEAU: In the mouth.

DR. JACOBI: What I am about to say is something that everybody knows, but perhaps it cannot be repeated too often—that is, that taking the temperature in the mouth is unreliable. In some patients this may be absolutely reliable, but in most of them it is not. It depends upon closing the lips over the thermometer and upon the condition of moisture of the lips. I never use it in the mouth without telling the patient to wet the lips thoroughly, and even then I find that the air may sometimes get into the mouth. There is only one place to take the temperature reliably, that is in the rectum, and even there we must remember that there is a difference of 0.5° between the temperature taken just inside the sphincter and that taken two inches higher up. In some instances it is easy enough to introduce the thermometer into the vagina, but, as a rule, the rectum is to be preferred. We should remember, too, that the normal temperature in the morning and in the evening differs about 0.5°. I would like to ask, also, what are the doses of tuberculin the doctor generally uses.

DR. TRUDEAU: I have found that for surgical cases you need rather a larger dose than for visceral tuberculosis. The reason is, probably, that the reaction is due to the explosion of the tuberculin stored in the lesions; and in the lungs, where the lesions are scattered and surrounded by numerous blood-vessels, the reaction is much quicker than occurs with lesions in the bones or where they are localized in a testicle or a joint. I always begin with one milligram, follow this with three, and then six.

DR. JACOBI: I am very sorry I have to speak of trite matters, but there is something else, namely, the finding of prolonged expiration and dulness, and the finding of retraction of the lung at the apex; these alone certainly do not prove anything. It may be simply the result of an interstitial pneumonia gone through with when very young. I know some patients that I observed with pneumonia in childhood, and whom I know now as adults, who show these symptoms as the result of that pneumonia and not the result of tuberculosis. Such cases must certainly give Dr. Williams dark shading in his X-ray pictures, for in such lungs there is in the previously diseased area a diminished air space and an increased amount of tissue.

DR. TRUDEAU: Such a case as that I would submit to the tuberculin test, and we have had several cases of that kind where tuberculosis was suspected, but failed to show up under this test. The X-ray cannot, of course, differentiate between a tuberculous and non-tuberculous consolidation.

SOME CONDITIONS OTHER THAN AORTIC ANEURYSM WHICH DETERMINE THE OCCURRENCE OF THE TRACHEAL TUG.

By HENRY SEWALL, Ph.D., M.D.,
OF DENVER, COLO.

Since the brief note of Oliver[1] in 1878 announcing the occurrence of the tracheal tug in aneurysm of the aorta, and the method for detecting it, the value of the phenomenon as a diagnostic sign has been somewhat in dispute. Macdonnell,[2] using a large clinical experience, committed himself to the statement that "tracheal tugging is never present except in aneurysm." Ewart,[3] Toulmin,[4] and others have found, on systematic examination of persons not the subject of aneurysm, that a more or less pronounced tracheal tug is present in a large proportion of cases, and Ewart found it more common in males than in females. Auerbach[5] and others have shown that the presence of tumors in certain situations about the aortic arch can cause the tug, and Norris[6] has recently reported a case in which the sign was prominent, without postmortem examination revealing physical conditions explaining it.

The excuse for the present paper is, first, that the deductions here presented are based on a much greater number of cases than seems to have hitherto been applied to the subject; second, I venture to believe that a satisfactory explanation of the tracheal phenomenon both in physiologic and in most pathologic conditions has been demonstrated.

[1] Lancet, 1878, vol. ii. p. 406.
[2] Ibid., 1891, vol. i. p. 535.
[3] British Medical Journal, 1892, vol. i. p. 596.
[4] Journal of the American Medical Association, 1897, vol. xxix. p. 4.
[5] Abstract in American Journal of the Medical Sciences, March, 1901, p. 340.
[6] American Medicine, March 20, 1901, p. 108.

My attention was first definitely directed to the tracheal tug as a diagnostic sign in the case of a gentleman who, for four or five years preceding his death, at the age of sixty, had suffered from a purulent bronchitis, in the abundant expectoration of which tubercle bacilli could only be demonstrated during the last year of life. This patient was racked by paroxysms of a loud, rather ringing cough; the aortic heart-sound was much accentuated; the pulmonary signs seemed to indicate pressure by an intrathoracic mass, and during the last year or more of life there developed a very distinct tracheal tug. A tentative diagnosis was made of intrathoracic tumor, malignant (in former years a supposed sarcoma had been removed from the breast), glandular, or aneurysmal, complicating tuberculosis. At the autopsy no tumor was found. The lungs were voluminous and contained rather few scattered tubercles, but there was striking thickening and stiffening of the bronchioles and pulmonary bloodvessels, with massive induration of the root of the left lung. In addition, the left pleura was throughout closely adherent to the chest wall.

On reflection there developed a simple and interesting explanation of the occurrence of the tracheal tug as dependent on the anatomical conditions discovered at the autopsy. When the aorta, looped over the left bronchus, presses upon the air tube sufficiently to transmit to it a pulsation, the downward stroke of the pulsating artery is expended both upon the trachea and on the upper lobe of the left lung. The lung tissue is normally of such extreme extensibility and its surface glides so readily on the thoracic wall that any ordinary impulse transmitted by the aorta to the bronchus stretches the lung tissue rather than pulls down the relatively fixed trachea. On the other hand, when the left lung is anchored, as it were, to the chest wall as if by close pleural adhesions, and when in addition the normal extensibility of the pulmonary tissues is diminished by infiltration or fibrosis, the pulse of the aorta must be registered by movements of the trachea to an increased amount compensating for the lessened mobility of the lung. Moreover, just as the lever of the sphygmograph performs wider excursions as the pressure of its spring on the artery is increased, so we should suspect systolic downward pulsation of the trachea to manifest itself especially under physiologic conditions in which the approximation of the aorta to the bronchus where it crosses the latter is closest.

In order to test the validity of this reasoning I have, during the past year, examined 430 persons as to the possession of a tracheal tug. No selection whatever was made as to the kind of cases studied. They included normal individuals, as well as subjects of diseases other than known aortic aneurysm. In each case the personal history was ascertained and in nearly all a physical examination of the chest was made. Though it would be desirable to have a far greater number of cases on which to base conclusions, I have to express grateful appreciation for assistance afforded me by many colleagues and friends. Very slight experience made it evident that a downward pulsation of the larynx immediately following systole of the ventricles is an extremely common phenomenon. These laryngeal movements form, as regards their amplitude, a continuous series varying from a just perceptible impulse transmitted to the fingers of the observer at the end of inspiration, to a strong downward twitch of the larynx approaching in vigor the tracheal tug in an appropriate case of aneurysm. I have never seen in any of my subjects so marked a tug as that developed in some examples of aortic aneurysm. But every aneurysm and its signs must have a beginning, and the diagnostic importance of the tracheal tug should depend largely for its specific value on being manifest when the other signs of aneurysm have not yet reached their full development. Many observers must have been struck with the gradual disappearance of the tracheal tug in cases of aneurysm in which, by one means or another, aneurysmal pulsation has been diminished by deposit of fibrin. The suspicion, of course, suggests itself that at least the slighter impulses here described are nothing more than the shocks of carotid pulsation transmitted to the larynx. In answer to this it may be said that the impulse or twitch can only be felt when the fingers are applied to the larynx in such a way as to detect a downward jerk; it is not observed on simply touching the front or sides of the cartilages. Moreover, the impulse is not brought out by firm backward pressure upon the larynx. To obtain the tug, the procedure originally proposed by Oliver cannot be improved upon; the patient should be seated, with the head well thrown back. This position elevates the larynx and puts the trachea on the stretch, so that downward impacts are less likely to be lost. The observer, standing behind the patient, places the tips of either his fore or middle

fingers under the rim of the subject's cricoid cartilage and presses gently upward. Sometimes only the thyroid cartilage can be satisfactorily grasped. Under these conditions the whole larynx is felt to make an inspiratory excursion downward, with a return upward in expiration, and a more or less evident tug may sometimes be felt, usually, but not always, confined to the phase of inspiration. The downward respiratory movement of the larynx becomes very marked with deep inspiration, and when the chest is fixed in this phase of respiration the larynx tends to become rigidly fixed in its lowest position. The downward movement of the larynx is said to be due to the inspiratory contraction of the sternothyroid and sternohyoid muscles. The extraordinary prominence of this movement in conditions of dyspnea and its frequent lethal significance in disease seem to be out of proportion to the benefits that can be ascribed to the movement. Although the non-aneurysmal tracheal tug tends to be confined to the phase of inspiration, the downward movement of the larynx in this condition, and, in fact, any fixation of the larynx by its extrinsic muscles, evidently must interfere with the mechanical conditions permitting the transmission of the movement of the trachea to the larynx. It has frequently occurred in the course of my observations, particularly with subjects of a nervous disposition, that a laryngeal twitch which was prominent at the beginning of an experiment completely disappeared when the patient's attention was directed to the respiratory movements. This anomaly was for a time attributed to possible variation in the amplitude of the aortic pulse, or even to change in the elasticity of the pulmonary parenchyma such as West[1] has suspected may arise from contraction of its intrinsic muscle fibers. Finally, however, the simpler and more satisfactory explanation was hit upon that the failure of the larynx to transmit the pulsatile movements of the trachea is due to such depression of the former organ through its sternal muscles as to relax the membrane connecting the rim of the cricoid with the trachea.

The general results of my observations are thrown together in a table at the end of this paper, but they may be made clearer by the following statements: In the table the results of the examinations as to the presence or absence of the signs of tracheal tug are classi-

[1] Allbutt's System of Medicine, vol. v. p. 338.

fied in the vertical columns according to the prominence of the sign. In the column headed "none" are placed the cases manifesting no pulsatile tracheal movement. In the column "slight" are cases in which only a slight pulsatile twitch was felt. In the column "d" the tracheal twitch was distinct, and the distinctness of the sign was more and more pronounced in the cases in the succeeding columns until in d''' the prominence of the tug might well lead to the suspicion of the existence of a developing aneurysm of the transverse portion of the aortic arch. It may be remarked that in my list three cases in which there could be no fair suspicion of aortic aneurysm exhibited a slight "diastolic shock," which Hall[1] believes to be pathognomonic of aneurysms of the aorta. My subjects varied in age from three years to eighty-five years. The youngest person manifesting a tracheal tug was sixteen years old. The tracheal sign was found relatively most frequent in persons between twenty and fifty years old, the age of greatest frequency being somewhat more advanced in cases having pulmonary disease. Of the 430 cases, 245 were males and 185 were females. The sexes are kept separate in the table, for reasons which will appear later. In order to test the efficiency of the conditions previously discussed to produce a tracheal tug, all cases were divided into three groups: I. Normal individuals, or those in which there was no evidence of left-sided pleural adhesions or pulmonary fibrosis. II. Cases manifesting the signs of tuberculosis at the left apex or giving distinct history of the disorder; also cases which had suffered pleurisy or pneumonia on the left side. III. Cases of marked arterial fibrosis or emphysema, including chiefly persons advanced in years. The cases were also grouped according to age.

It is assumed that cases in Class I. had lung tissue of normal elasticity and were without pleural adhesions; that in the members of Class II. there were probably pleural adhesions on the left side as well as probably diminished pulmonary extensibility; in Class III. the extensibility alone of the lung tissue was assumed to be affected.

Of the 245 males examined 113 are recorded as normal as regards their pulmonary condition. Of these 61 manifested no tracheal twitch, and 52, or 46 per cent. of the 113, exhibited a twitch. No

[1] American Journal of the Medical Sciences, January, 1900.

less than 37, or + 32 per cent. of the 113, exhibited a very evident tracheal tug of varying degrees of distinctness. Of 112 males showing evidence of pulmonary lesions, probably causing adhesions of the left pleura, only 17 were without signs of the tug, while 95, or 84 per cent., possessed it, and 71, or + 63 per cent. of the 112, showed a very prominent tug.

A striking exception to the occurrence of the tracheal phenomenon in pulmonary disease was found in some tubercular cases in which extensive excavation occupied the site of the left upper lobe of the lungs. This apparent anomaly rather supports the position here assumed as to the conditions determining the transmission of the tug, for when a large mass of pulmonary tissue is absent the bronchus distributed to it cannot be supposed to be fixed on the side of the lung. Also, it is worth observing that in two cases of left-sided pneumothorax (accompanying tuberculosis) there was no tug whatever. Of the male cases of the third class, those showing signs leading to a suspicion of greatly diminished extensibility of the pulmonary tissue, there were 20 examples. Of these 10, or 50 per cent., showed a tug, a proportion differing little from that found in normal cases; but of the 10 cases, in 6, or 30 per cent., the tug was of a decided character.

NUMBER OF PERSONS SHOWING VARIOUS DEGREES OF TRACHEAL TUG.

	Age in years.	Males, 245.						Females, 185.					
		None	Slight	d	d′	d″	d‴	None	Slight	d	d′	d″	d‴
I. Persons normal or without evidence of pulmonary disease.	0 to 10	3	...	...	...	...	...	2					
	11 " 20	5	1	6	1	1	1	15	4	...	...	...	1
	21 " 30	10	6	12	6	3	...	51	8	4			
	31 " 50	29	6	5	...	...	...	22	7	3	1	1	
	51 " 70	13	2	2	...	...	...	7	1				
	Over 70	1	...	...	...	...	...	2					
II. Persons showing evidence of having had tuberculosis, pneumonia, or pleurisy of the left lung.	0 to 10												
	11 " 20	...	...	1	...	...	...	2	1	1			
	21 " 30	7	8	16	9	2	6	6	7	4	1	...	1
	31 " 50	10	13	10	16	4	5	4	5	5	2	1	2
	51 " 70	...	2	...	1	1	...	...	1	1	2		
	Over 70	...	1	...	...	...	...	1					
III Persons showing marked emphysema arteriosclerosis.	0 to 10	1											
	11 " 20												
	21 " 30	...	...	1	1	...	...	1	...	1			
	31 " 50	3	2	...	...	...	...	1					
	51 " 70	5	1	1	1	...	2	3	...	1			
	Over 70	1	1										

A comparative study of the 185 female cases leads to interesting conclusions. In 125 normal persons 99 were found without tracheal twitch, and 30, or + 23 per cent., with it. Of the latter only 10, or less than 10 per cent. of the whole, showed anything like a distinct tracheal tug. On the other hand, of 47 female cases with probable left pleural adhesions, 34, or + 72 per cent., manifested pulsatile tracheal movement, which in 20 cases, or + 42 per cent. of the 47, was marked in character.

In the third class of females there were but 9 cases, showing a tug in 4, or 44 per cent.

The conclusion is manifest that *a tracheal tug quite palpable in character is, in the majority of cases, associated with and dependent upon adhesions of the left pleura. Diminished extensibility of the lung tends to produce the same phenomenon, and the tug is most pronounced when the conditions are combined.*

It still remains to explain why perfectly normal subjects so often exhibit a distinct laryngeal jerk following the heart-beat. This fact seemed to me a mystery until, in the course of observations, a satisfactory explanation developed.

It is noteworthy that the proportion of normal males manifesting the tracheal sign is exactly double that of females of the same class, whereas the difference between males and females having pulmonary lesions is not nearly so marked. Now, the type of masculine respiration is diaphragmatic, while that of feminine breathing is costal. In downward movements of the diaphragm the heart also descends to some extent,[1] and thus, it may be supposed, draws the aortic arch closer upon the left bronchus, and thus improves the chances for the transmission of its pulsation to the trachea. After this explanation it is clear why healthy females should fall so far behind normal males in the frequency of the tracheal pulsation. It is also to be expected that the tracheal phenomenon should, in its milder manifestations, be confined to inspiration. It is easy to prove, on anyone exhibiting the tug and having good control over the respiratory muscles, that the tracheal jerk accompanies inspiration by the descent of the diaphragm, but that it is absent when air is drawn into the chest only by elevation of the ribs.

[1] F. H. Williams. Medical Uses of the Röntgen Light. American Journal of the Medical Sciences, June, 1899, p. 678.

A second conclusion may therefore be drawn from these observations, namely, *that in the normal individual descent of the heart with inspiratory movement of the diaphragm may so press the aortic arch upon the left bronchus as to impart to the trachea the aortic pulse, recognizable at the larynx as a palpable tug of greater or less distinctness.*

THE EXTENSION OF AORTIC ANEURYSMS INTO AND BETWEEN THE WALLS OF THE HEART AND DISSECTING ANEURYSMS OF THE HEART.

By LUDVIG HEKTOEN, M.D.,
OF CHICAGO.

(From the Pathologic Laboratory of Rush Medical College.)

The relations to the heart of aneurysms in the beginning of the aorta are often quite interesting and complex. Interparietal and intraparietal extension may occur, and many so-called dissecting aneurysms of the heart take their origin in the beginning of the aorta.

Dissecting vascular aneurysm is the result of an incomplete rupture of the arterial wall from within, through which the blood by its hemodynamic pressure separates more or less extensively the various layers of the wall. The separation is a rather rough one, there being no real dissection. The walls of the heart are not disposed to this change, because the force or pressure that causes the separation originates in the walls of the heart during their contraction when the various layers are pressed together (Vestberg).

Partial cardiac aneurysms are oftener the result of a uniform dilatation of a weakened area than of rupture and dissection. There are, however, quite a number of places where and methods whereby dissecting cardiac aneurysms may be formed by the separation of layers normally more or less adherent to each other. The aneurysm need not originate primarily in the cardiac cavity whose walls largely contain it; it may come from other cavities or from the aorta. The sinus of Valsalva may give origin to dissecting aneurysms which extend into the walls of the heart, because, though properly a part of the heart, they are not affected by the physiologic limitations for aneurysmal formation seen in other parts of the heart (Vestberg). Aneurysms in the beginning of the aorta may extend into the heart, and on the rupture of the original sac secondary cardiac aneurysms of the dissecting variety may

develop. Cardiac aneurysms, apparently dissecting, originating in myocardial abscesses, sometimes are not dissecting aneurysms, strictly speaking, because the larger part, yes, even all the dissecting, may have been done by the suppuration ; hence, dissecting cardiac aneurysm cannot be separated always from aneurysm following myocardial abscess. With the foregoing considerations in mind, Arthur Vestberg,[1] in his interesting and complete study of dissecting aneurysms of the heart, defines dissecting cardiac aneurysm as a pathologic cavity communicating with the heart or with the origin of the aorta, due to a separation by the blood of the layers of the walls of the heart.

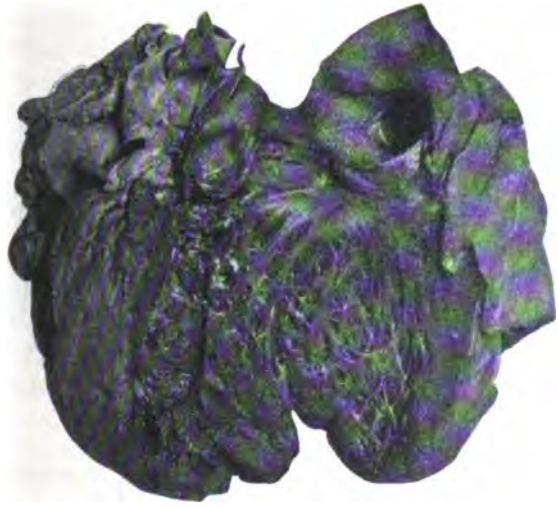
Vestberg divides dissecting cardiac aneurysm into interparietal, septal, parietal, and valvular, the first being by far the most frequent. Of 60 cases (59 from the literature and 1 original) 47 were interparietal or septal, 5 parietal, and 8 valvular. The interparietal is an interesting form, which occurs in the loose tissue under the epicardium around the root of the aorta. Vestberg, who is the first to give an accurate description of this periaortic space, designates it spatium periaorticum cordis. It is bounded externally by the anterior walls of the auricles and by conus arteriosus dexter ; internally or centrally by the aorta, the root of the aorta, and the more or less incomplete conus arteriosus sinister. The roof of the space is formed by the epicardium passing from the posterior surface of the aorta to the anterior surface of the auricles and constituting at the same time the floor of sinus transversus pericardii. The space is divided by the coronary arteries into the auriculo-aortic and the conoaortic parts (spatium atrioaorticum and spatium conoaorticum). The points of exit of the right and left coronary arteries are designated by Vestberg as apertura spatii dextra et sinistra. It will be seen at once that the space belongs to the heart and that aneurysms occupying the space must be regarded as cardiac provided they do not possess independent walls from other sources. Ruptures may occur into the periaortic space from conus arteriosus sinister, the sinuses of Valsalva, the lower part of the aorta, and probably from the coronary arteries. Rupture of the aneurysm of the left coronary artery, described by Dr. J. A. Capps[2] in my laboratory, might have resulted in a dissecting aneurysm of the heart, most likely of the parietal type. The thinnest portion of the internal wall is the fibrous part of the conus arteriosus sinister with its prolongations upward between the aortic valves. Vestberg describes a dissecting aneurysm of the peri-

[1] On dissekerande hjärtaneurismer, Nordiskt Medicinskt Arkiv, 1897, Ny Följd, vii., Nos. 26 and 30.

[2] American Journal of the Medical Sciences, September, 1899.

aortic space following rupture due to endocarditis of its internal wall between the base of the anterior mitral valve and the aortic valves. Endocarditis, abscess, sclerosis, and other changes in the beginning of the aorta and the aortic sinuses, traumatic ruptures, and the secondary rupture of aortic aneurysms may lead to dissecting aneurysms in this space. The openings are often linear, especially when traumatic, and round when the result of ulceration. At first there may be no distinct wall, but in chronic cases a membrane may form. From the periaortic space the dissection may extend into the interventricular and interauricular septa, the interparietal aneurysm becoming septal. Occasion-

FIG 1.



Aneurysm of aortic sinus with extension into wall of right ventricle.

ally it becomes parietal. Secondary ruptures into the pericardium, especially at the orifices of the space—the exits of the coronary arteries —as well as into the right heart may take place.

The following specimens illustrate many of the features in connection with this form of dissecting cardiac aneurysm and the relation to the heart of aneurysms in the beginning of the aorta.

Laborer, aged thirty years, syphilitic; death from typhoid fever. Aneurysm of anterior aortic sinus with extension into wall of right ventricle; beginning aneurysms of aorta.

Anatomic Diagnosis (Dr. Crowder). Typhoid ulcer and swelling of Peyer's patches; gumma in epididymis; arteriosclerosis; aneurysm of

sinus of Valsalva extending into wall of right ventricle; beginning aortic aneurysms with thrombosis; fibrous perisplenitis and pleuritis; pulmonary edema; chronic nephritis; edema of ankles; stricture of urethra; acute cystitis; suppurative prostatitis; catarrhal gastritis.

The sinosal aneurysm arises in the sinus behind the anterior aortic valve, the orifice of the right coronary being situated near its bottom; it is 3 cm. in depth and extends into the tissues under the epicardium over the anterior surface of the right ventricle under the apex of the right auricle (Fig. 1). The wall is thin, smooth, extensively calcified, sections showing degenerated fibrous tissue without elastic elements. About 9 cm. above the aortic valves is a brown, circular area, 1 cm. in diameter, which is much thinner than the surrounding

FIG. 2.

FIG. 3.

FIG. 2.—Small sacculation in aorta, showing wrinkling of thinned spot.
FIG. 3.—Small sacculation in aorta, showing thinning of media.

tissue and thrown into folds (Figs. 2 and 3), but on outward pressure with the finger a small sacculation is formed. A little higher up is a smaller area of similar appearance and occupied by a thrombus.

Sections across the depression and including some of the aorta on each side and also the corresponding part of the pulmonary artery, which here is closely apposed and closely adherent to the aorta, show no changes in the pulmonary artery; its elastic network seems perfect. At the point of greatest bulging of the aorta the tissue between the aorta and the pulmonary artery is reduced to a thin layer of hyaline fibers; a few bloodvessels are present and also some greatly flattened and compressed nerves; there are but few nuclei in the hyaline tissue and no cell accumulations. On each side of the aortic bulge there is interposed between the two vessels fibrous tissue with areas of fat, nerve bundles, and bloodvessels. Many of the arterioles show a well-marked

fibrous, obliterating endarteritis and hyaline adventitia. In some complete occlusion has taken place.

Corresponding to the aneurysmal bulging the aortic wall is thrown into folds of varying depth; the endothelium is absent; the wall is thinner by about one-half than on each side of the aneurysm; there is hardly any normal muscular tissue in this part of the aorta; the wall consisting of a more or less degenerated fibrous tissue with but few nuclei, often distorted and with a tendency to assume a bluish tinge in hematoxylin. This fibrous tissue is in reality the greatly thickened intima. There are no foci of cells in this part, but in the media on each side of the bulging are a few thin-walled vessels filled with blood and surrounded by quite marked cellular infiltrations. The cells have deeply stained round or oval rather small nuclei, and the cell bodies cannot be distinguished. There are no elastic fibers immediately around these perivascular accumulations.

The intimal thickening does not give any elastic fiber stain. There are a few irregular, broken-up bundles and masses of elastic fibers between the thickened intima and adventitia at the bottom of the aneurysm. In the sections stained for elastic fibers it is seen clearly how the media is gradually replaced by the thickened intima, the media ending in narrow strands of elastic tissue. The elastic fibers in the adventitia are also largely interrupted over the bulging. The arteries with endarteritis obliterans in the tissue between the pulmonary artery and the aorta show a well-developed network of elastic fibers in the new tissue in the intima.

In the smaller aneurysm with the thrombotic plug the conditions outlined above are present in exaggerated degree. There is a marked intimal thickening with degeneration. There is a more sudden interruption of the media, which is completely replaced by the intimal thickening as the outward bulging takes place, on each side of which are masses of broken-up elastic tissue. And the vascularization and round-cell infiltration into the media are more pronounced and associated with similar changes in the adventitia. Owing to the cellular infiltration in the media the elastic elements are broken up extensively. Among the cells in the perivascular infiltrations are seen plasma cells, lymphocytes, and endothelial cells. The thrombus is infiltrated with leukocytes; no bacteria present.

Bacteriologic Examination. B. typhosus isolated from the spleen; B. coli from the liver and kidney.

Abstract of Histologic Description. The liver contains necrotic foci. There is some increase of the connective tissue in the kidneys and the

cells of the convoluted tubules are degenerated; there is some endarteritis. There is myocardial disunion. The spleen contains many phagocytic cells; there are also areas of necrosis. The cell accumulation about the base of the ulcer in the ileum contains endothelial cells with cellular inclusions. There is a chronic interstitial epididymitis with obliteration of the vessels as well as foci of leukocytes and epithelioid cells.

One of the cases of aneurysm of the coronary arteries described by Capps[1] presents some features of interest in connection with this subject.

Man, telegrapher, aged thirty-nine years, syphilitic and alcoholic, died from bronchopneumonia developing during hemiplegia and convulsions.

Anatomic Diagnosis. Syphilitic leptomeningitis and pachymeningitis; arteriosclerosis; aneurysm of the aorta and of the left coronary artery; chronic aortic endocarditis; fibrous myocarditis; aneurysm of interventricular septum; hypertrophy of the heart; chronic nephritis; bronchopneumonia; fibrous pleuritis.

The heart weighs 550 grammes. There is marked thickening of the left ventricular wall. The tricuspid, pulmonary, and ventral valves appear normal. The endocardium is smooth, excepting that the free margin of the aortic valves is rough, thickened, and sclerosed. Just below the junction of the left and anterior semilunar valves is a small bulging in the septum, which admits the tip of the index finger, and is lined with a dense fibrous tissue. Anteriorly the aneurysm and the sinus of the posterior pulmonary valve are separated only by a thin partition, which is translucent. The "undefended space" situated to the right of this cavity is unaffected.

Above the left aortic semilunar valve is a bulging of the aortic wall upward and forward into the periaortic tissue. Bordering on this aneurysm is the left coronary orifice, which is of normal size. Immediately beyond the opening, however, is a fusiform dilatation of the wall of the coronary artery, large enough to contain a hazel-nut, and extending for the most part posteriorly and to the right. Its walls are streaked with yellowish spots, and in places calcareous scales can be peeled off. Beyond this cavity is a second and smaller dilatation of the wall.

The beginning of the aorta is much thickened, the intima irregularly fissured, and similar changes exist throughout the entire thoracic aorta. The microscopic examination showed principally chronic changes with calcification.

[1] Loc. cit.

The presence of syphilis in these two cases brings forward the relations of syphilis to aneurysm. This is a vexed question. Heller[1] champions the existence of a pure syphilitic aortitis that may cause aneurysms. Peculiar circumscribed depressions, often in groups, especially at the beginning of the aorta, in which the aortic wall is greatly attenuated and wrinkled, with cellular accumulations about the vasa vasorum and destruction and replacement of the elastic and muscular elements of the media, are regarded as the result of a primary syphilitic mesaortitis by Heller and his pupils.[2] In such lesions so-called miliary gummas with giant cells are described by Backhaus and others. Weber has described a gumma as large as a bean in the wall of the pulmonary artery. Backhaus found mesaortitis of this character in seventeen of ninety-nine syphilitics examined at the Kiel Institute. Irregular ulcerations in the aorta with callous margins are also attributed to syphilis. When combined with ordinary arteriosclerosis the aortic wall may be greatly thickened, uneven, and wrinkled. This is the sclerogummous aortitis of Malmsten, who gives the frequency of syphilitic history in aneurysm as 80 per cent. In 82 per cent. of eighty-four cases of general paralysis Straub[3] found the changes described by Heller as syphilitic aortitis. Straub also records the presence of giant cells and gummous productions in the media. In some of these cases were aneurysms with peculiar punched-out orifices. Of seventy-one non-paralytics examined during the same period such changes were found in the aorta but seven times, all in syphilitics, however. Ponfick,[4] Ziegler,[5] and Orth[6] doubt the syphilitic character of all instances of this kind of aortitis because similar changes occur in non-syphilitics. Baumgarten[7] also assumes a clinical attitude. Ziegler and Babes[8] hold that ordinary microbes, as streptococci and staphylococci, may produce lesions similar to those ascribed to syphilis. The changes described in the aorta of Case I. correspond well to Heller's syphilitic aortitis, upon the basis of which it is probable that aneurysms in young syphilitics arise. Perhaps the nearest approach at the present time to the truth in regard to syphilis and certain aortic lesions and aneurysms is embodied in the Scotch verdict, "guilty but not proven."

The beginning aneurysms in the aorta in Case I. show in an interesting manner the histogenesis of aneurysm, destruction of elastic elements in the media, thickening with new formation of elastic fibers in the

[1] Verh. deut. path. Gesellsch., 1900, ii., 346–351.
[2] Döhle, Dissertation, Kiel, 1885.
[3] Verh. deut. path. Gesellsch., 1900, ii., 351–363.
[4] Ibid. [5] Ibid. [6] Ibid. [7] Ibid. [8] Ibid.

intima, and dilatation. It is rare that one has the good fortune thus to trace the starting of aneurysm. Rupture of the aneurysm of the aortic sinus might have given rise to parietal dissecting aneurysm of the right ventricle. This event is illustrated in a striking manner by the following specimen in the collection of the laboratory, which also shows the gross changes regarded as indicating the syphilitic nature of certain aortic lesions and consecutive aneurysms.

Two sacculated aneurysms of aorta and aneurysm of aortic sinus with interparietal and intraparietal extension into heart (Fig. 4). *Dissecting aneurysm of periaortic space. Museum specimen; no history.* The heart

FIG. 4.

Three sacculated aneurysms of the aorta and aneurysm of aortic sinus, with interparietal and intraparietal extension into the heart.

as a whole is somewhat enlarged, especially the left ventricle. The right heart with its valves is normal. The muscle is of a healthy color. The aortic semilunars are thin and transparent. The beginning of the aorta is dilated somewhat, the intima thick, irregularly nodular and furrowed, and extensively sclerotic. Upon the right and posterior aspects are the openings of three aneurysms. The smallest opening is situated just above the junction of the right posterior and anterior valves; the aneurysmal cavity is situated in the periaortic space between the aorta and the right ventricle and auricle; it measures 4 cm. transversely and 7 cm. vertically; the bottom of the cavity rests upon the interventricular septum; at the top the thin roof of the periaortic space

is raised quite high. The opening from the aorta into the aneurysm is situated about at the center of its posterior wall. The cavity is empty. There is no trace of the wall of the aorta recognizable in the walls of the aneurysm, sections of which show a layer of quite structureless material in the lining, outside of which are a loosely arranged fibrous and fatty tissue with irregular fragments of elastic fibers.

The orifice of the second aneurysm is a long transverse slit on the posterior surface of the aorta, a little above and to the left of the former. This leads into an irregular cavity composed of two arms—a short one that passes toward the right, and a long one which passes to the left and downward for at least 4 cm. into the space between the left auricle and the aorta and under the pulmonary artery. The two aneurysms are separated from each other by the descending vena cava, which is closely bound to the aorta at this point. A section of the wall, which is quite thin and covered with thrombi, shows a fibrous structure with a few irregular elastic fibers.

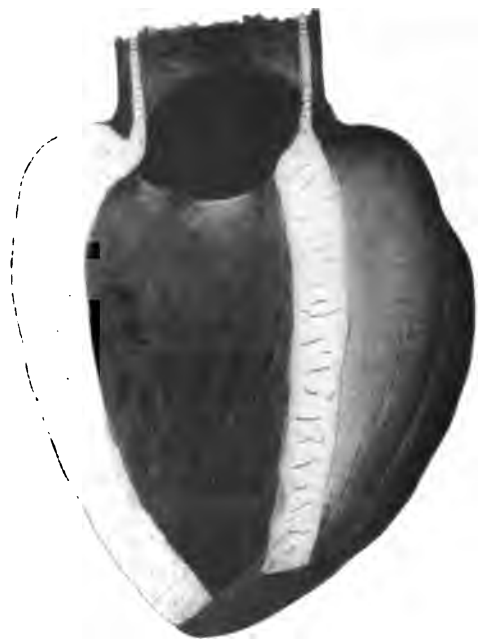
The third aneurysm starts in the sinus behind the left posterior valve. The cavity is somewhat irregular and extends into the wall of the left ventricle and along the interventricular groove for 3 cm. At the apex the wall is translucent. The left coronary artery opens at the margin of the aneurysm; its descending branch is normal, but the main stem is obliterated for about 2 cm. as it courses over the aneurysm. The aortic wall is recognizable throughout in this aneurysm.

This interesting specimen illustrates at one and the same time interparietal and intraparietal extension of aortic aneurysms into the heart and the secondary formation of dissecting aneurysms in the periaortic space.

Large parietal aneurysm of the right ventricle originating in sinuses of anterior and right posterior aortic valves (Figs. 5 and 6). *Museum specimen; no history.* The heart is much enlarged, the pericardial cavity wholly obliterated, the aorta extensively sclerotic and calcified. The aneurysm originates immediately behind the anterior and left posterior valves by an opening 4 cm. in diameter. Viewed from within the aneurysm the aortic orifice appears triangular. The aneurysm seems to have dissected its way in the wall of the right ventricle, extending from the aorta between the right auricle and the pulmonary artery to the apex of the ventricle covering the anterior and lateral aspects of the latter. The right auricular appendix is embedded in the wall of the aneurysm. At the apex muscular tissue and subepicardial fat are readily recognized upon the external surface of the aneurysm, and outside of these is a well-marked layer of fibrous tissue—the adherent

pericardium. The lining of the aneurysm is almost universally calcified, fissured, roughened, and cracked. On account of the calcification the aneurysmal walls do not collapse but remain stiff, being easily separable into more or less structureless layers in which are also calcareous scales; and there are continuous sheets of calcareous material in the pericardial adhesions for some distance beyond the bounds of the aneurysm. The cavity is empty. There are no definite traces of aortic wall beyond the opening. Microscopic sections from various parts show a structure-

FIG. 5.



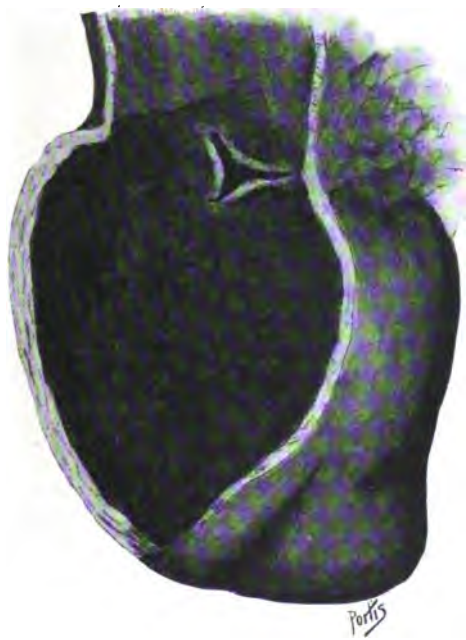
Large parietal aneurysm of right ventricle originating in aortic sinuses (anterior view).

less wall consisting largely of calcareous material covered externally, especially at the apex, by a layer of fibrous tissue containing a dense layer of elastic tissue like that in the epicardium.

The following specimens are examples of endocarditis of aortic valves as related to dissecting cardiac aneurysm. In the first the beginning of the condition is shown, while in the second and third destruction of the internal wall of the periaortic space has been followed by a typical dissecting aneurysm in its conoaortic part.

Acute endocarditis of the aortic valves, developing in the course of lobar pneumonia in a man, aged thirty-seven years, destroyed a large part of the left posterior valve, causing an extensive perforation of the segment and extending from the ventricular aspect of the valve to the interventricular septum (Fig. 7). In the septum there is an irregularly oval, ulcerated excavation, covered by detritus. The ulceration has extended upward between the myocardium and the aorta and has

FIG. 6.



Large parietal aneurysm of right ventricle originating in sinuses of aortic valves (posterior view).

reached the lower part of spatium periaorticum (Fig. 7). Microscopic sections through the affected area show about the ulcer an extensive inflammatory infiltration, with numerous colonies of bacteria; the inflammatory changes extend far out into the myocardium and are especially marked in the tissue of the periaortic space.

The pneumococcus was isolated in pure culture from the vegetations and ulcers.

Acute and chronic endocarditis of aortic valves; dissecting aneurysm of the periaortic space (Figs. 8 and 9). The left posterior aortic valve

is thick and fibrous, and the part near the anterior segment is extensively destroyed, tattered, and shreddy. The right posterior valve shows an oval, irregular ulcer on the ventricular surface. The anterior valve is largely destroyed; it is perforated by an opening, 1 cm. in diameter, from the aortic sinus, and the remaining ventricular surface is covered by granular thrombotic depositions. The triangular space between the anterior and left posterior valve presents an opening coextensive with the space and reaching up to the upper limit of the attachment of the valves upon the wall of the aorta. This opening leads into a smooth walled, empty cavity, situated between the aorta and the pulmonary conus, and the beginning of the pulmonary artery. This cavity extends

FIG. 7. FIG. 8. FIG. 9.

FIG. 7.—Extension of aortic endocarditis to interventricular septum.
FIG. 8.—Acute aortic endocarditis; dissecting aneurysm of periaortic space.
FIG. 9.—Aneurysm of periaortic space following acute endocarditis.

to the right and to the left for a short distance from the margins of the opening in the root of the aorta; the prolongation to the left shows a tendency to extend into the interventricular septum. The lower margin of the aneurysmal opening, which rests upon the top of the interventricular septum, is quite smooth. The undefended space is not involved in the lesion. The aneurysm does not communicate with any other part of the heart than the left ventricle. No trace of aortic tissue is demonstrable in its walls, which in places show a necrotic surface with leukocytic and cellular infiltration, especially around micrococcal masses, in the deeper layers. Micrococcal masses are also present in the granular and necrotic layers on the surface.

Acute streptococcus and chronic endocarditis of aortic valves; perforation of internal wall of periaortic space and beginning dissecting aneurysm. This occurred in a man, aged thirty-four years, who died from erysipelas

and acute streptococcus infection of the aortic and mitral valves during the course of chronic aortic endocarditis. The left posterior and anterior aortic curtains are extensively ulcerated and perforated, and in the triangular space between the two halves is a ragged opening extending into the periaortic space, the walls of which are dissected so as to form a small cavity.

A FURTHER REPORT ON A CASE OF PRESYSTOLIC MURMUR ASSOCIATED WITH PREGNANCY, ETC. ORIGINALLY REPORTED AT THE MEETING OF THE ASSOCIATION IN MAY, 1899.

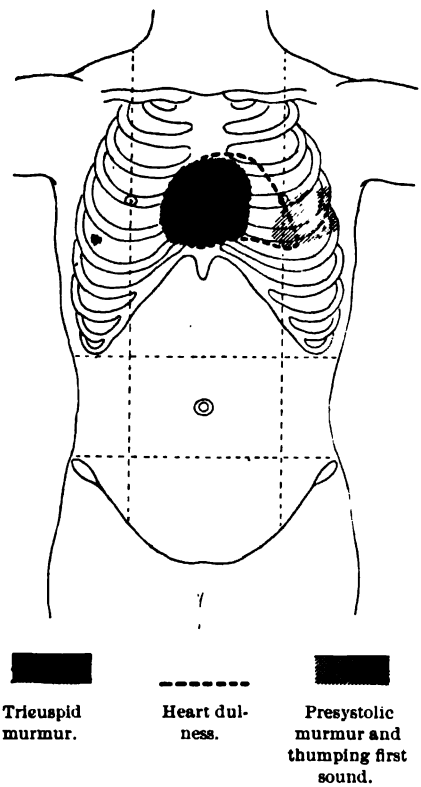
By JAMES TYSON, M.D.,
OF PHILADELPHIA.

It may be remembered that I read before the Association at its meeting in May, 1899, a short account of a case of presystolic murmur associated with systolic tricuspid murmur complicating pregnancy in a woman who was admitted to the Hospital of the University of Pennsylvania with these symptoms and condition. In addition she had a striking jugular pulse simultaneous with systole of the ventricles, a marked presystolic thrill at the apex, and increased area of cardiac dulness. There was a thumping first sound characteristic of a case of mitral stenosis, with sharp accentuation of the pulmonic second. There were associated aggravated dyspnea and distressing cough, emaciation and exhaustion, but no dropsy except the amniotic dropsy. The physical signs are illustrated by Fig. 1. With the birth of her child came, as was to be expected, marked improvement of all symptoms, including disappearance of the jugular pulse, replacement of the apex, and probably slight change in the situation of the right border. An enlarged liver could now be recognized. At the date of my first report to the Association her breathing rate was 20, her pulse 60, and the temperature 97.2°, these being approximately the temperature, pulse, and rate for three days previous. She was discharged thus improved June 21st, and a month later went to work in a shoe factory, and continued to work a part of each day until Christmas, 1899. She could not, however, do a full day's work because of shortness of breath easily induced, an irrepressible drowsiness at times, faintness, and sometimes syncopal attacks. Soon after

the new year 1900 she grew worse, and was readmitted to the hospital January 16, 1900.

Physical Examination on Readmission. Negative as to all organs excepting the heart. There is visible pulsation over the left precordium, and the apex-beat is visible and palpable, somewhat irregular, in fifth interspace slightly outside the nipple line. A presystolic

FIG. 1.

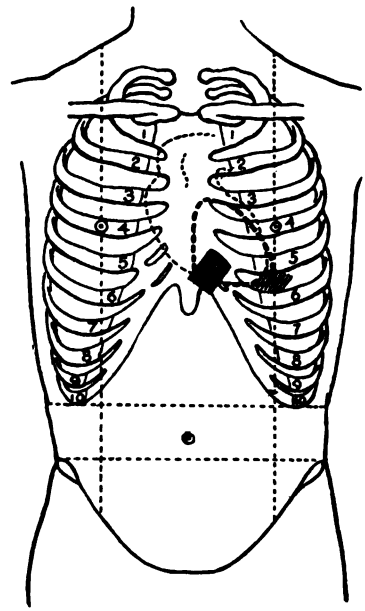


On readmission, March 16, 1899.

thrill can be felt. Absolute cardiac dulness begins at the lower edge of the third rib, to the left of the sternum, that of the right border, between mid-sternum and left edge of sternum. Auscultation recognizes a short, rough, presystolic murmur at the apex, terminating in a sharply accentuated, thumping first sound, the first part of diastole

being also occupied by a murmur. At the tricuspid area a distinct systolic murmur is heard, conducted a short distance to the left of the sternum toward the apex, growing fainter as the latter is approached. There is also heard at base a markedly accentuated pulmonic second sound. (See Fig. 2.)

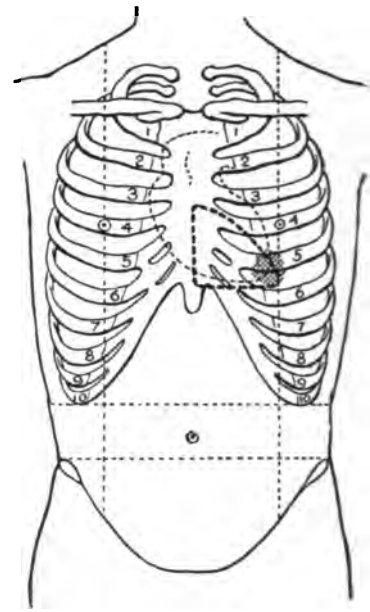
FIG. 2.



Tricuspid murmur. Heart dulness. Presystolic murmur and thumping first sound.

On admission, January 16, 1900.

FIG. 3.



Presystolic murmur and thumping first sound. Heart dulness.

On readmission, February 1, 1901.

On April 5, 1900, the following note was made:

Mrs. McC. has been quite comfortable for some time, being up and about the ward. For purposes of examination she is again put to bed. Her temperature and pulse-rate have been normal for some weeks; her breathing-rate has varied between 20 and 27. On inspection we find chest symmetric, well nourished, and a scarcely appreciable prominence of the left precordium. Apex-beat is not visible, but

can be felt in fifth interspace in nipple line. At this time there is no thrill palpable, but sometimes under agitation there has been a thrill since her return to hospital. Relative cardiac dulness is recognized at lower edge of third rib to the left of sternum, and at the right in the mid-sternal line. Absolute cardiac dulness at the upper edge of the fourth rib and at the left edge of sternum. Auscultation recognizes only a very short presystolic murmur, ending in an exaggerated thumping first sound; this is much less marked than originally. At this time no diastolic murmur except the presystolic is heard, nor a systolic at apex, nor a systolic at ensiform, although there was at time of readmission and at times since. Pulmonic second sound is sharply accentuated in strong contact with aortic sound. She menstruates regularly and has gained seven pounds since her admission.

She was again readmitted February 1, 1901, having had a cold all winter and grippe early in January, when she went to bed and remained there until admission to hospital. Before the grippe she had at times a smothering sensation, especially when she went up stairs rapidly. During the grippe her lungs filled up and there were copious expectorations, sometimes bloody, especially recently. She could not sleep lying down, and had a few fainting spells. Her feet were swollen once.

On readmission her pulse was 80, breathing 26, and temperature 98.6°. She was somewhat dyspneic, but soon improved after resting, and in a few days seemed quite well. Evidently her condition was vastly improved as compared with the first and even second admission. The physical examination the next day recognized trifling prominence of the left precordium, breathing 20, pulse 78, temperature 97.4°. There was no thrill appreciable in mitral area; the apex-beat was in fifth interspace, mid-clavicular line. There was no presystolic mitral murmur, no systolic mitral murmur, or tricuspid murmur. There remained, however, a thumping first sound at apex, though less marked than at previous admissions, growing rapidly fainter as the sternum was approached and disappearing at the third rib, where the pulmonic element of the second sound was well heard. Percussion found relative dulness to the left of the sternum, at lower border of the third rib, absolute dulness on the fourth rib; for the right border relative dulness at right border of sternum absolute at about mid-sternal line.

Fig. 3 indicates the area of dulness at the third admission, and the shading at the apex the seat of the thumping first sound. There was, as mentioned, no mitral murmur and no presystolic murmur, although at times the latter seemed to come out culminating in the thumping first sound.

There were in addition, on admission, some physical signs of the pulmonary engorgement, which was responsible for her more serious symptoms at this time, but these rapidly passed away, and she was discharged March 20, 1901, much improved, the last weeks of her stay being rather because I desired her to remain in the wards than any real necessity for her so doing.

It is not very usual to have an opportunity to examine a cardiac case at such long intervals and exhibiting so strikingly different stages in returning compensation as this, which furthermore illustrates typically the changing physical signs of mitral stenosis.

ORCHITIS AND EPIDIDYMITIS IN TYPHOID FEVER.

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THE especial intention in the present paper is to record the clinical histories of two cases illustrating a rare complication or sequel of typhoid fever.

Orchitis or epididymitis occurring as a complication or sequel of typhoid fever was first alluded to by Velpeau[1] in 1844. An incomplete case was reported by Chedevergne[2] in 1868, and the first complete case by Hanot[3] in 1873. Westcott,[4] in 1898, had collected 32 cases, and in the same year Eshner,[5] after a thorough search through the literature, was only able to find 44 cases, which have been analyzed by him in an interesting paper. The rarity of the lesion is also indicated by the fact that in Pierre Do's *Thèse de Lyon*,[6] 1899–1900, on Epididymo-orchitis of Typhoidal Origin, the statistics of complications occurring in 14,738 cases of typhoid fever, drawn from French and German sources, show no record of any instance of epididymitis or orchitis. In Osler's[7] series of 829 cases of typhoid fever, published in 1900, orchitis or epididymitis was observed only in two instances, both unattended with suppuration; and in the 889 cases treated in the Presbyterian Hospital from 1892 to 1901 in my colleague's services and my own, this lesion was noted only in the two instances related in the present paper.

It is probable that the frequency of this complication is greater than the statistics indicate. Aside from cases which presumably have not been reported, the fact that in the 44 cases collected by Eshner,[5] 5 occurred after the second week of convalescence, 1 of these as late as the ninth week, suggests the presumption that cases occur in which the true origin of the orchitis is not suspected.

The two cases which form the subject of the present paper occurred

nearly simultaneously in my service in the Presbyterian Hospital during the past winter, and the interesting opportunity was afforded of studying and comparing their different clinical histories.

CASE I.—D. S., male, aged twenty-four years, was admitted to the Presbyterian Hospital in my service on January 30, 1901, apparently on the seventh day of his illness. The previous diagnosis of typhoid fever was confirmed after admission. The Widal test gave a positive result on the tenth day of the disease. The infection was of a moderately mild type; the maximum temperature did not exceed 104.5°, and there was only slight mental disturbance. The treatment was the customary one, viz., the cold bath. The illness was an uneventful one, without complications. The morning temperature was normal on the twenty-first day of the illness, and both morning and evening temperatures were normal on the twenty-third day. The leukocyte range was unusual both during the course of the fever and later in convalescence in the presence of a sequential lesion. On admission the leukocyte count was 8000 and remained at about this point until the fifteenth day of the patient's illness, when it rose to 14,000. There was then little variation until the eighteenth day, when the count was 11,000, and from this date it gradually but continuously receded to 7000. The increase in the number of leukocytes occurred without appreciable cause, and the decrease continued in the presence of a lesion during convalescence.

The urine was examined every other day during the patient's stay in the hospital. A faint trace of albumin was present from admission until February 21, the twenty-ninth day from the beginning of the illness, but at no time were casts found. The catheter was not used during the patient's stay in hospital, and there was at no time any urethral discharge. There was no history or evidence of gonorrheal infection in the past.

On the fifth day of normal morning and evening temperatures the patient complained of slight pain in the right groin, and on examination what appeared to be a swollen gland could be detected. The temperature rose to 101°. On the following day the apparent swollen gland was found to be the cord, enlarged, hard, and sensitive, in the inguinal canal. The following day the swelling had reached the external ring, and in the course of the succeeding twenty-four hours the morbid process had extended to the epididymis and testicle.

The cord could now be palpated, swollen, hard, and sensitive throughout the inguinal canal into the scrotum to the epididymis. The epididymis and the testis proper became markedly swollen and very sensitive. There was no effusion into the tunica vaginalis.

Almost simultaneously with the appearance of the swelling of the cord, pain and tenderness were developed in the upper portion of the long saphenous vein. The phlebitis gradually extended along the course of the vein to the lower part of the leg, and was attended with moderate swelling of the leg and thigh.

The swelling and tenderness of the cord and testicle gradually subsided, and on discharge from hospital, on the sixteenth day after the first appearance of the symptoms, the only evidence of the testicular lesion consisted of a slight induration and sensitiveness of the epididymis. The temperature remained slightly above normal until the eleventh day after the development of the orchitis and phlebitis of the saphenous vein. There was still sensitiveness along the course of the saphenous vein and moderate swelling of the leg and thigh on the patient's discharge.

The study of other cases of orchitis occurring in the convalescence of typhoid fever indicates that the lesion is, as a rule, attended with little constitutional disturbance. The persistence of the fever in the present case was attributed to the concurrent phlebitis of the saphenous vein. Bacteriologic examination of the urine was not made.

On examination of the patient on April 20th, ten weeks after discharge from hospital, all physical signs of a lesion of cord, epididymis, and testicle were absent. The leg and thigh were still slightly swollen, but tenderness on palpation along the course of the saphenous vein had disappeared. The patient complained, however, of pain along the course of the vein and of tenderness in the testicle after much standing or walking.

CASE II.—A. S., male, aged thirty-four years, was admitted to the Presbyterian Hospital, in my service, December 18, 1900, apparently on the fourteenth day of his illness. On admission the Widal test gave a positive result, the spleen was palpable, there was a copious and characteristic typhoid eruption, the leukocyte count was 8000. There was no history of venereal disease in the past, there was no urethral discharge, and a catheter was not used during the patient's illness. The infection was of a mild type. The maximum temperature was 104°. There was no mental disturbance, and a normal morning temperature was reached on the tenth day after admission, apparently on the twenty-fourth day of the illness. Both morning and evening temperatures were normal on January 2d, the thirtieth day of the illness.

The urine on admission contained a small amount of albumin and a few hyaline and granular casts; and similar conditions were noted until January 10th. On December 31st, a very considerable number of leukocytes were found in the urine, and a slight degree of pyuria continued to be present until January 10th. From this date examinations of the urine were negative until the discharge of the patient from hospital, January 30th.

With the development of the pyuria there was a rise of temperature, maximum 102°, which persisted during its continuance. From January 10th there were normal morning and evening temperatures until January 14th, when the evening temperature rose to 101°. Two days later the temperature was normal and remained so until the patient's discharge from hospital.

Coincident with the last rise of temperature the patient complained of pain in the right testicle. On the following day the scrotum was reddened, the epididymis and testis proper were both involved, being greatly swollen

and acutely sensitive. The epididymis was especially affected. The cord apparently was not implicated. The inflammatory symptoms rather rapidly subsided, and on January 30th, the date of discharge, the only remaining sign of the lesion was a slight tenderness and induration of the epididymis. The urine was not examined for typhoid bacilli.

The patient was readmitted on February 26th. A week after discharge from hospital there was a recurrence of pain in the right testicle, which again became swollen and sensitive. These conditions persisted until his re-admission.

On admission the temperature was normal, the right half of the scrotum was reddened and greatly swollen. On palpation, both the epididymis and testicle were found to be swollen, hard, and exquisitely sensitive. At one point over the testis proper fluctuation was appreciable. There was no effusion into the tunica vaginalis. The cord, double its normal size and very hard to the feel, could be traced from the epididymis to the external ring and throughout the inguinal canal.

On examination by Dr. Tilden Brown, the seminal vesicles were found to be insensitive and apparently of normal size. The prostate was slightly enlarged, but not sensitive on palpation. The ordinary urinary examination was entirely negative, and bacteriologic examination of the urine failed to reveal Eberth's bacillus.

Aspiration at the point of fluctuation was made, and a small amount of pus was obtained. The bacteriologic examination of the pus by Dr. Tuttle, the assistant pathologist of the hospital, demonstrated the presence of Eberth's bacillus in pure culture.

The swelling and sensitiveness of the testicle, epididymis and cord have very slowly subsided.

The cord, two months after the readmission of the patient, can be palpated as far as the internal ring; it is hard, nearly double the size of the cord of the opposite side, and slightly sensitive. Both the testicle and epididymis are still very hard to the feel, and a small sinus leads to the body of the testis, through which minute shreds of necrotic tissue are occasionally extruded.

In the 53 cases[8] of testicular inflammation occurring in the course or during the convalescence of typhoid fever, which comprise the literature of the subject, suppuration developed in 13. Bacteriologic examination demonstrated the presence of Eberth's bacillus in pure culture in the pus from 6 of the cases.[9] In a single instance[10] pyogenic cocci alone were found. The remaining 6 cases[11] were reported prior to or about the date of Eberth's discovery of the specific bacillus of typhoid fever.

In 1 non-suppurative case[12] Eberth's bacillus was obtained in pure culture from the serosanguinolent fluid withdrawn by an aseptic puncture of the testicle.

In view of the bacteriologic findings, the *usual* origin of orchitic lesions in typhoid fever cannot be doubted. Apparently only exceptionally is the infection due to other micro-organisms than Eberth's bacillus. It remains to consider the probable channels of infection.

It is probable that the bacilli reach the testicle both by the blood-stream and from the urethra through the intermediary of the vas deferens. That Eberth's bacillus in great numbers is found in the urine in a large percentage of cases of typhoid fever is now well known.

In Case I., of those whose clinical histories have been given, the pathologic process evidently originated in the cord within the inguinal canal or at a point above it, and thence gradually extended to the epididymis and the testicle.

It will be recalled that it was possible to trace the *gradual* progress of the lesion, the epididymis only being affected forty-eight hours after the cord was palpable (swollen, hard, and sensitive) in the canal. The prior implication of the cord suggests an original infection either of the vas or of the spermatic veins, producing a phlebitis with thrombotic formation and a secondary implication of the vas by contiguity. The nearly simultaneous development of a phlebitis of the internal saphenous vein suggests the possibility of a similar lesion of the spermatic veins. It will be recalled that the internal saphenous vein receives the external pudic which crosses the spermatic cord.

In Case II. the infection affected the epididymis and testicle to the exclusion of the cord in the first attack. It was acutely involved in the recrudescence.

It may be of interest to analyze briefly Eshner's 44 cases[5] and the 9 additional ones,[8] which I am able to add, of orchitis and epididymitis occurring in the course or during the convalescence of typhoid fever, comprising all cases found in the literature of the subject which give sufficient detail to be of value.

Sixteen cases developed during the course of the fever: of these, 1 occurred during the second week; 6 during the third; 2 during the fourth; 1 during the fifth; 1 during the sixth; 2 during the seventh; 2 at "defervescence;" 1 at time not definitely stated.

Thirty-five cases developed during convalescence: of these, 11 developed during the first week; 7 during the second; 3 during the third; 1 during the fourth; 1 during the fifth; 1 during the

sixth; 11 at a time not definitely stated. In 2 cases the date of development is not given.

In 2 cases the inflammation affected both sides, in 45 it was unilateral, and in 6 cases no statement is made of its localization.

Of the unilateral cases, 22 were on the right side, 21 on the left, and in the remaining 2 it is not stated on which side.

The epididymis only was involved in 7 cases; the testicle only in 16 cases; both epididymis and testicle, in 26 cases; and in the remaining 4 a distinction is not made between the testis proper and the epididymis.

There was effusion into the tunica vaginalis in 9 cases; in 10 it is noted that such effusion was absent; and in 34 no statement is made on this point.

Suppuration occurred in 13 cases, partial necrosis in 5 cases, complete necrosis in 2 cases, atrophy of the testicle in 1 case, and death in 2 cases, but without apparent relation to the complication.

Recovery, with residual nodules in the epididymis, is noted in 17 cases; the subsequent histories of these cases would be of interest.

The bacteriologic examinations of the pus in the suppurating cases have been given earlier in this paper.

A study of these cases justifies the following conclusions:

1. Epididymitis or orchitis occurring in the course or during the convalescence of typhoid fever is a rare lesion and is of typhoidal origin.

2. Only very exceptionally is it due to secondary microbic infection.

3. It develops at a late period in the disease or during convalescence.

4. The lesion, although as a rule unilateral, may be bilateral, and involves either the epididymis or testicle, or both, and not infrequently the cord.

5. Effusion into the tunica vaginalis is rare.

6. Termination most often is by resolution.

7. Suppuration occurs in 25 per cent. of all cases.

8. Localized necrosis and extrusion of testicular tissue are not uncommon.

9. Exceptionally there is destruction of the entire testicular structures.

10. Atrophy of the testicle occurs, but is a rare sequence.
11. The lesion gives rise to little constitutional disturbance.
12. Death as a direct result of the lesion has not been noted.

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DISCUSSION.

DR. OSLER: As illustrating the very late occurrence of this complication, I may refer to a case at present under my care. The man had typhoid nearly three months ago, and about two weeks ago he was admitted with orchitis on the left side. The typhoid bacillus was found in the urine during the course of the disease, but he went out of the hospital without it, and the examination was negative on his return.

DR. SHATTUCK: The first example of this that I ever saw happened in my service at the Massachusetts Hospital last autumn. Curiously enough, I believe three cases occurred at the same time in the service of Dr. Fitz on the opposite side of the hospital.

DR. MUSSER: One of the patients admitted to the University Hospital late in the course of typhoid, recently had an orchitis which we attributed to the typhoid. His primary attack of typhoid was so mild that he had not even gone to bed, but the orchitis brought him down.

DR. WILLIAMS: I would like to add another case which occurred in my service at the City Hospital last autumn.

DR. BAUMGARTEN: As these cases seem rare, I may mention one seen last year in private practice. It occurred in a young boy, aged sixteen years, who had passed through an ordinary attack of typhoid fever. The orchitis occurred during the fifth week of the typhoid, and was preceded by an inflammation of the internal saphenous vein.

THE NATURE OF INTERNAL LESIONS IN DEATH FROM SUPERFICIAL BURNS.

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THE cause of death in superficial burns is so obscure that even indirect evidence is worthy of consideration, and a few points are here indicated which favor the supposition that a toxemia is produced which in its effects is largely similar to the toxemias of bacterial origin. It is not the object of this paper to discuss that problem, but to put forward some points which may augment our knowledge of the lesions of this condition, which have been very carefully described by Bardeen in an article published in 1897 in the *Journal of Experimental Medicine* and further elaborated in the *Johns Hopkins Hospital Reports*, vol. vii. Therein he has described the visceral changes which occur, laying particular stress upon the effects produced in the lymphatic system. In the most advanced state he finds the centers of the lymphatic follicles everywhere in a condition which he describes as necrotic, indicated by a broken-up condition of the germinal and surrounding regions, where bits of deeply-staining chromatin and granular vacuolated protoplasm are scattered about, the whole being underlaid by a background of large, flattened cells similar to the reticulum and the cells which line the lymph sinuses; these are phagocytic, and rapidly engulf the débris. Phagocytosis seems also to be carried on by the larger leucocytes. It is this picture which illustrates his interpretation of the term focal necrosis, which is to-day so variously construed by different observers.

The similarity of his findings in every one of five cases which he examined was so great as to favor the view that these focal necroses

are a characteristic lesion in the lymphatic tissue. The cases which are here dealt with indicate that damage to the lymphatic tissue always occurs (where life has been prolonged after the burning), but that the extent of this, even in severe cases, may fall short of the stage of focal necrosis. The lymphatic tissue sustains injuries which vary in degree but not in kind, a variation due to differing tissue resistance or to differing strength and amount of toxin ; and while a single case may indicate, as we would expect, various stages of damage, even to focal necrosis, yet a given case need not show any of these extreme effects. We cannot lose sight of the fact that lymphatic tissue engaged in a constant struggle with toxins and other enemies of the body will practically never be free from the changes produced by slight irritations, and that this variability will be powerful in preventing the occurrence of a characteristic lesion. Although the pathologic facts cited may not be definite and clear-cut, attention may be directed to the striking similarity they bear to the effects of the chemical toxins of the better known bacterial diseases.

The series consists of seventeen cases, in five of which I was able to make the postmortem examination, obtaining full lymphatic material ; from four others I was able to obtain the superficial glands (generally inguinal, under a burned area), although autopsy could not be performed ; for the eight others I depended upon the autopsy reports of the Montreal General Hospital for 1900, and was able to obtain material from the organs which were kept as a matter of routine, but which in only one case included lymphatic glands. Six cases were in children under six years—one was twelve years old, the rest adults. Three died instantly, two lived five hours, one seven hours, five twenty-four hours or less, one thirty hours, the longest duration of life being eight days. At autopsy the intestinal tract was noted as healthy in six ; in four various degrees of mucosal injection were observed ; in one duodenal ulcers, two in number, were found ; in five the brain or meninges showed change ; in three the respiratory system or some part thereof was affected ; five showed general congestion of organs ; two cloudy swelling of organs ; in two only was marked glandular enlargement noted. The glandular tissue examined consisted of mesenteric and bronchial, superficial and deep inguinal glands.

The particulars of cases are given briefly as follows :

CASE 1.— Female, aged six years, lived twenty-four hours.

CASE 2.—Male, aged twelve years, burned by caustic soda, lived thirty-five hours. Congestion of internal organs; almost entire destruction of superficial layers of skin; thrombosis of superficial vessels; pulmonary apoplexy; ecchymosis of pericardium.

CASE 3.—Male, elderly, lived five hours. Mesenteric glands enlarged, soft, and on section caseous; pulmonary tuberculosis.

CASE 4.—Male, aged three years, lived twenty-four hours. Spleen congested; high degree of nephritis.

CASE 5.—Male, aged four years, lived sixteen hours. Edema and congestion of brain; acute gastritis; moderate nephritis.

CASE 6.—Female, aged twenty-four years, lived eighteen hours. Congestion of lungs; localized areas of gastritis and enteritis.

CASE 7.—Female, aged four years; lived four hours. Hyperemia and congestion of brain, spinal cord, and meninges; congestion of abdominal organs.

CASE 8.—Male, adult, lived less than twenty-four hours.

CASE 9.—Female, middle-aged, lived five hours. Injection of meninges; spleen and liver swollen and "cloudy."

CASE 10.—Female, aged forty-five years, lived thirty hours.

CASE 11.—Female, aged twenty months, lived ninety-six hours. Edema and congestion of brain ; pallor of organs.

CASE 12.—Female, aged thirty-three years, lived eight days. Several small areas where mucosa of stomach is absent (autopsy twenty-six hours after death), around which is injection of vessels; duodenum congested.

CASE 13.—Female, aged twenty-eight years, lived ninety hours. Three cm. from pyloric ridge are two duodenal ulcers; mesenteric glands enlarged; Peyer's patches granular and raised; localized enteritis.

CASE 14.—Female, aged forty years.

CASE 15.—Female, aged forty-two years.

CASE 16.—Female, aged twenty years.

In all three of these cases burns of third degree; no lymphatic changes.

CASE 17.—Female, aged seven months. Lymph glands enlarged; thymus very large; congestion of brain, meninges, and lungs.

In the three cases spoken of as dying instantly (dead when removed from a burning building), the lymph glands showed no change, and death having probably been due to suffocation they may be dismissed without further comment. The lymphatic glands examined in the six other cases exemplify two conditions, or, it may be, two stages of the same process. The more striking of the two (I hesitate to call it the more advanced) shows the follicle with cleared central portion, and densely packed periphery, a condition

sometimes demonstrable in a section to the naked eye ; the less evident degeneration is diffuse, scattered, and apparent only upon close microscopic observation. The former, indicating a definite focal change, was represented in the series by Cases 11 and 13 (the latter a child of twenty months, living ninety-six hours after infliction of the burn). As Bardeen has described, the follicle presents a striking picture, the center contrasting strongly with the periphery. In the periphery the densely-packed blue leukocyte-nuclei make a dark surrounding ring, the center being a strongly contrasting pink.

Area of proliferation and phagocytosis in lymph gland. Especially notable is the freedom of this area from fragments and the large irregular nuclei of the endothelial cells.

This central portion consists of large, flat, slightly granular cells, thrice the diameter of a lymphocyte, of various shapes, triangular, quadrilateral, multipolar, and some even almost circular. These last-named appeared to be free, and those of the irregular shapes to be stationary and to form part of the reticulum of the gland. The region of these cells seemed to be singularly free from nuclear fragments, the nuclei of the cells themselves standing out distinctly and mostly round, although on closer inspection a few bladder-like nuclei are seen, in which the chromatin is coarsely reticulated.

The cell bodies belonging to these last nuclei are very hard to demonstrate.

Cell inclusions in the fixed cells I have not seen, although the free cells frequently show contained lymphocytes, each inclusion apparently occupying a vacuole. If we compare these large cells with the stroma cells of a normal lymph gland we find that the former are larger and more granular, although in every lymph gland from which the lymphocytes have been shaken out there are cells which are identical in appearance. If, as we suppose, these cells are the proliferated endothelial cells of the reticulum or of the capillaries (enlarged and multiplied under the stimulus of a toxin of moderate intensity), it is not at all strange that we should find them in lymphatic tissue which we call normal, for if we consider the conditions to which lymphatic tissue is at all times exposed it can be readily understood that slight irritations are constantly in health stimulating the lymphatic tissue, the greater number of these cells in the glands in toxic conditions intimating a greater intensity of toxin. All evidence seems to be in favor of the view that these proliferated endothelial cells are phagocytic, both in their free and their fixed state (although, as I have said, I saw no evidence of phagocytosis of the fixed cells). On no other supposition can the rapid disappearance of all traces of cellular débris be explained.

In the periphery of the follicle the presence of these cells could not be made out, for a sudden transition occurs from the clear area of endothelial cells to the margin where the lymphocytes are so densely packed as to prevent any other cells being seen. All these lymphocytes, though aggregated in greater numbers than usual, are practically normal.

In the second class of cases, which comprised the larger part of the series, no focal changes were evident, but there were in each one indications of a more diffuse, less violent change in the lymphatic tissue. At various parts of the gland careful search will show fragmented nuclei, degenerating lymphocytes, the large endothelial cells just described, and at times these large cells partially degenerated. In these sections there is no difficulty in finding inclusions in the large free cells. Although under high powers of the microscope these conditions are found in various parts of the

lymphatic tissue, the glands viewed under a low power convey no idea of a high grade of degeneration.

The explanations afforded of the cause of this breaking up of cells in the region of the germinal centers is not a very satisfying one. The supposition that death is caused by the formation of toxic substances in the blood, due to breaking-down of tissue substance, bears with it considerable weight. It lies outside the scope of this paper, yet one may go so far as to say that the lesions found strongly suggest such a condition.

When one finds the region immediately surrounding the point of emergence of the blood from the capillary in a state of necrosis, the idea immediately arises that a toxic condition of the blood has caused it. It has been suggested that there has been a great outflow of blood from the capillary by which the cells are excited to destructive activity. The phase "destructive activity" is often upon our lips, but, like too many others, has no rational basis. The mother cell, truly enough, may sacrifice its existence to its progeny, they in turn to their progeny, but when reproductive force is expended, and the ultimately produced cells can no longer reproduce, they do not die but rather cease to reproduce. The biologist sees in the cell the counterpart of the more complex organism, and there is no real reason why we should attribute functions to the one that are utterly at variance with the practice of the other. Therefore, a more rational explanation of the destruction of the germinal center of the lymph follicle is that an actual poison is poured out of the capillaries, and in its most undiluted form strikes the cells of the germinal centers first, and exerts upon them its greatest effects, viz., a sudden killing and immediate disintegration of the cell.

It may be urged that this toxin ought first to affect the cells of the capillaries. It doubtless does, urging them to proliferation of the endothelial cells, the newly-formed cells being thrown into the capillaries and constituting the free large granular cells of which we have spoken above. Should it be further urged that the toxin which can kill a lymphocyte can kill an endothelial cell, we can point to the proliferated endothelial cells at the center of the follicle, which appear to be in a resistant living state, while the lymphocytes which once occupied the same region have been overcome.

It must doubtless be that the "cleared-center" state of the lymph follicle is a later stage than the so-called "necrotic center" condition; but the question arises here, have the lymphocytes really been killed by toxins? or have they fallen victims to the phagocytic power of the enormously proliferated endothelial cells? It is probable that both factors have been at work, though the question must remain an open one. Rather in favor of the all-conquering power of the endothelial cells are Metchnikoff's observations upon the phagocytosis of lymphocytes by the endothelial cells in normal digestion in the intestinal villi, and as indicating in the enlarged and multiplied endothelial cells a state of activity hardly consistent with true necrosis there may be cited a point which appears in the study of the sections of the intestine of Case 13. In the solitary lymph follicles of the intestine and in the Peyer's patches which are enlarged there appear similar "cleared" areas in which endothelial cells only are to be seen (saving a few lymphocytes) exactly like the areas described in the lymphatic glands.

In some places so much do the follicles abut upon the intestinal lumen that the "cleared area" is separated from the intestinal lumen only by an infinitesimally narrow barrier, consisting of a dozen layers of lymphocytes.

If this follicle be, *as it appears to be*, in a state of "necrosis," it is to be expected that infection by bacteria will occur, with consequent destruction and ulceration. All indications point to the fact that these so-called focal necroses exist in the lymph follicles of the intestine in a fair percentage of cases. Yet intestinal ulcers, especially in the lower parts of the small intestine, are not a feature in death by burns. In the absence of subsequent ulceration, can we consider these as true necroses? I think not. Bardeen's own high power photomicrograph, published in the articles spoken of, shows the area of so-called necrosis, covered by débris, but underlaid by the endothelial cells. It is, therefore, not with his observations that issue is taken, but with his interpretation. This condition of tissue indicates, I think, not true necrosis (the result of intense continued toxemia), but rather "proliferation and phagocytosis, the result of weaker, more dilute toxins," if I may borrow Mallory's term; and by phagocytosis we must here under-

stand not only phagocytosis by the endothelial cells, but also the more familiar leukocytic phagocytosis.

According to the appearance of these "cleared areas" the action of the lymphatic gland appears to be this: The first line of defence consists of the lymphocytes and leukocytes as seen in a normal gland. In opposing the toxins this first line of defence is broken up and overcome, but the same attack which overcomes the first line of defence stimulates and calls into existence the second line of defence—*i. e.*, the enlarged proliferated endothelial cells, which in turn oppose the toxins, and, to judge by the resistant appearance of these cells, do so successfully. It is not to be supposed that the lymph gland, with its second line of defence thrown into the breach, is stronger than at first, for very little increase of toxic power might suffice to turn the scale; but the point is, that such a gland is not in a necrotic but in an actively resistant state.

In assisting us to an understanding of the pathology of the condition these large endothelial cells are a very important point, for they are found not only in the lymphatic glands and in the intestinal follicles, but also in the capillaries of the liver of several of the cases cited here. Mallory's work upon these cells leads us to suppose that their wide-spread occurrence in toxic conditions is by no means yet fully recognized. In the present observations I have found them in the liver of cases of death shortly after accident, in the lymph glands of peritonitis, in the spleen of cerebro-spinal meningitis, in the spleens of myocarditis and of chronic tuberculosis; in fact, in conditions which have little in common. In the recently published monograph of Councilman, Mallory, and Pearce on diphtheria, as well as in the earlier work of Mallory upon the lesions of typhoid fever, these cells have been described, and the last-named author in an article on "Proliferation and Phagocytosis" referred to them as a result of moderate toxemia. To them I must acknowledge the explanation of these cells at a time when the finding of them in various conditions and in various organs had proved a great difficulty. The existence of these cells, so exactly similar to those found in the lymphatic lesions of diphtheria, seems to be a strong argument in favor of the action of a toxin of a chemical nature circulating in the blood of the burned body. The existence of these cells elsewhere will be further commented upon.

Scarcely less interesting than the lymphatic lesions are the conditions apparent in the kidney. Finding in the kidneys of the cases of young children a great degeneration, it was forcibly apparent that the picture was here once more, that of an acute toxemia of a chemical nature, for the greatest lesions appeared in the glomeruli and in the upper parts of the convoluted tubules. In no one of the cases was the kidney unaffected, although in the two cases of advanced age the changes were partly interstitial, and irritation previous to the infliction of the burns had produced extensive changes. But in the cases of the young children the marks of an intense nephritis were present. The glomeruli showed considerable enlargement; so great, indeed, that frequently no capsular space could be seen, and where it was apparent there was frequently cellular débris present in the space, though fibrin was never seen. The glomeruli in all cases showed an excess of cells, very few of which were of the nature of blood cells, so that, presumably, the capillary endothelium had undergone great proliferation, although mitotic figures were not demonstrated.

The convoluted tubules in the majority of the cases were mere masses of cellular débris, with scarcely any nuclei apparent ; side by side with these were tubules with a high degree of hyaline degeneration. The descending loops of Henle and the collecting and discharging tubules generally showed no degeneration, and the interstitial tissue had not apparently suffered to any extent. Congestion was not especially marked. My attention not being directed sufficiently early in the work to the blood changes, the use of alcohol as a preservative prevents my speaking with any degree of certainty upon the occurrence of pigment in the organs.

From observation of these cases it would appear as if considerable stress should be laid upon the kidney condition as being always well advanced, although the lesions are in no sense characteristic of any condition other than a toxemia resembling that produced by chemical poison eliminated by the glomeruli and the convoluted tubules.

The localization of the tubular changes is strongly suggestive of toxemia in that the portions of the organ affected are those that possess a selective power, the tissue suffering while it excretes the toxins. In the liver six cases showed great intracellular deposit

of pigment in the cells of the central parts of the lobules ; four cases showed fatty infiltration of high degree ; one showed fatty degeneration, and one cloudy swelling of the cells, results which may be dwelt upon only as indicating once more the similarity to the condition found in toxic states. The point of interest was the appearance here of the large granular cells, similar to the free cells seen in the lymphatic glands. Here I found the notes I had made upon these cells corresponding entirely to those of Councilman, Mallory, and Pearce upon the cells found in the liver in diphtheria. Some of these cells were exactly similar to liver cells, but their nature was, to my mind, entirely proved by finding so many of them partially adherent to the cells of the endothelium of the capillaries as well as free therein. Many of these cells were long and narrow and so distorted as to give the impression of their having been under pressure at some recent time, the largest appearing 40 to 50μ in length. The occurrence of these cells in the capillaries is strongly suggestive of the belief that the wandering cells of the lymphatic areas are produced by the endothelium of the capillaries (as well as possibly by the proliferation of the fixed reticulum cells of the part). The "free" cells of the liver capillaries did not, as a general rule, show inclusions; but this may be due to the non-existence of necrosis in the liver, or to the fact that if these very cells had travelled from elsewhere in the circulation they had had time to complete the digestion of the cells they had devoured.

The intestines of some of the cases show upon gross examination swelling and prominence of the lymphatic follicles, and in Case XIII. (which had two duodenal ulcers) there were found the "cleared areas," as elsewhere in the lymphatic tissue, the large endothelial cells being again the prominent feature, and the region of these cells showing no nuclear débris.

The conditions found in the spleen scarcely call for further comment than to point out that the Malpighian bodies in Cases XI. and XIII. showed the "cleared areas," that the bodies were in most cases very prominent, and the intervening tissue frequently the seat of large deposit of blood-corpuscles, most of which appeared to be intact.

The question of the cause of death has been voluminously dis-

cussed by many writers, and so excellent a summing up of the literature has been made by Dr. Bardeen that further enlargement upon it is superfluous. Since that time but little is to be found upon the pathology of burns. C. Parascandolo[1] finds that injection of ptomains, extracted from the blood, muscles, and organs of burned animals, produces a condition in the cells of the nervous system which is not to be distinguished from that produced by infections.

In conclusion, the points which I would like to emphasize are these :

1. The entire pathologic picture presents great similarity to conditions found in the diseases characterized by the presence of toxins of bacterial origin in the blood.

2. Damage to the lymphatic tissue is a constant feature, but is not necessarily focal, some cases presenting only diffuse degeneration. The cases which live but a few hours after infliction seem more likely to present the "focal" condition than those which live a longer time, as the condition which I interpret as proliferation and phagocytosis is one which may rapidly disappear.

3. The focal lesions are not a true necrosis, but rather a proliferation of the endothelial cells of the reticulum and of the capillaries, and a phagocytosis of the leukocytes and endothelial cells, to which latter is due the fragmented, disintegrated appearance which suggests a true necrosis.

4. This "cleared center" state is an indication of an actively resistant though not unimpaired gland.

DISCUSSION.

DR. FLEXNER: This paper is a very welcome confirmation of Dr. Bardeen's studies, and also a very valuable addition to the results which he obtained. It is interesting to recall that the inciting agent to the study of this work by Dr. Bardeen was found in the similarity of the lesions observed at autopsy in a group of cases coming together with the lesions found by Dr. Welch and myself in experimental diphtheria in lower animals. The similarity was so striking that it was suggested to Dr. Bardeen to make a study of the lymph glands and other structures taken from widely different por-

[1] Archives de Physiol. Nor. et Path., Paris, 1898, 5 s., x. p. 714.

tions of the body, and he studied them with the results that Dr. Adami has mentioned. The lymph-gland changes that occur early are chiefly concerned with proliferation in the centers of the nodes and what we would take to be evidences of individual cellular necrosis. I am willing to adopt Dr. McCrae's views as to that being a phagocytosis, but if the process can be compared with that taking place in toxin infections we have in this a disintegration of the center of the nodule. It is a surprising picture, and one who has viewed burns in the light of toxemias can realize how similar they are.

DR. JACOBI: I would like to ask if there is any relation between these changes which have been demonstrated and the physical changes that take place in the blood after burns. The physical changes consist in the change of hemoglobin into methemoglobin. That the kidneys should be affected in such cases is, I believe, an old experience. When the blood is changed in that way, when large masses of methemoglobin are found, the first masses are found in the kidneys. That was the universal finding in the cases I described first, more than twenty-five years ago, of poisoning by chlorate of potassium. The same is true of other poisons. I attributed it to acute nephritis at first, not knowing at that time of the changed condition in the hemoglobin, which was first demonstrated, long after my first publications on the subject, by Marchand, in Halle, Germany.

DR. WELCH: I would like to say a word about the interpretation of these focal lesions. Of course, it is very gratifying that both of these studies have resulted in favor of the theory that the fatal effect of extensive burns is really due to some sort of toxin, and it is very likely that is the result of the local action of the heat upon the blood in the superficial capillaries of the body, for, of course, no one dreams that it is really produced by bacteria. As Dr. Flexner has said, we would be quite prepared to accept this view that the nuclear fragments are the result of the digestion of the epithelial cells by these large phagocytes. While it is not, of course, permitted to come to any definite conclusion from *a priori* arguments, I find some difficulty in thinking of such a theory as Dr. Adami has described. The sum of it is that the poison or toxin stimulates certain cells to proliferation, and these at once begin to dispose of the lymphoid cells in the neighborhood. I cannot understand how that can be, and it seems to me it would be better for nature to proceed to utilize these large phagocytic cells to dispose of cells previously damaged. These large endothelioid cells are supposed to be taking on a pernicious function and devouring the good cells to the extent of a further and needless damage to the body. We think of the toxin as doing the harm, and then let the endothelioid cells, which are thought of as more important cells than the phagocytes, step in and dispose of the previously damaged cells.

I do not think the important question hinges altogether on whether those fragments are produced one way or the other. There is simply a little diffi-

culty in my mind as to accepting the interpretation which Mallory and McCrae have given.

DR. ADAMI: I trust that Dr. McCrae's paper has not given the impression of serious divergence from Dr. Bardeen's views. On the contrary, Dr. Bardeen's article must be regarded as the basis upon which Dr. McCrae's research was developed—and Dr. McCrae arrives at the same conclusion, namely, that the changes in the tissues clearly indicate the existence of a toxemia, and this toxemia is to be regarded as a most important factor in the production of the disturbances which follow severe burns. Only he did not find the constant presence of focal necroses in the lymphatic glands, upon which Dr. Bardeen laid considerable stress. Here I may state that I do not regard it as impossible that the latter found actual necrotic conditions; it is to be noted that all his cases occurred in members of one family, and it may be that, as a family idiosyncrasy, the affection of the endothelial cells was severer in his cases than is usual, that necrosis followed enlargement and proliferation.

Dr. McCrae's sections show what are clearly various stages of enlargement and proliferation of the endothelial cells of the lymphoid reticulum. In answer to Dr. Welch's remarks, I would urge that several observations by different observers indicate that an irritant which will, for example, lead to the destruction of the lymphocytes may but cause the enlargement and proliferation of endothelial cells, and that we have evidence that under the influence of bacterial toxins these latter cells are peculiarly apt to show enlargement and to exhibit phagocytic functions. Indeed, we may legitimately suppose that these larger endothelial cells have greater power of resistance, and that toxins introduced into their neighborhood may stimulate the more resistant endothelial cells—"macrophages," as Metchnikoff has termed them, though I do not like the term—or to engulf the damaged leukocytes of the disturbed area.

NOTES ON THE TREATMENT OF SOME FORMS OF CANCER BY THE X-RAYS.

By FRANCIS H. WILLIAMS, M.D.,
OF BOSTON.

It is yet too early to make a report at length on the use of the X-rays in the treatment of certain forms of cancer, and I should not have presented anything at this meeting had I not felt bound to respond, though it must be very unsatisfactorily, to the invitation of our honored President to read a short paper.

It has been recognized for many years that certain forms of cancer, especially face cancer, can be relieved, sometimes temporarily and sometimes permanently, by the use of caustics or the actual cautery. It is also well-known that by the use of the X-rays we may produce burns. If we use the rays in such a way as to cause a burn, and good results are brought about, it does not follow that the X-rays have played any other part than that of a caustic. I wish to present to you, briefly, some of the cases which I have treated where the caustic action of the X-rays was avoided, and, therefore, it seems probable that the X-rays are responsible for the good results, and that we have in them a novel therapeutic agent that is useful in this as well as in other diseases.

It occurred to me that certain of my patients who were old and perhaps not very well nourished might have improved temporarily because of the care and diet received in the hospital, but further investigation showed me that this explanation would not hold, as most of them came from the out-patient department of the hospital or from my own practice, and, therefore, no change had taken place in their environment. The only new element introduced into their treatment has been the exposure of the diseased area to the X-rays for a few minutes daily, or, in some cases, for two or three times a week. The details of the method for carrying out this treatment,

and the precautions to be taken, are given in my book on *The Röntgen Rays in Medicine and Surgery*, which is now in press; but perhaps it will be well to state here that while any risk of an X-ray burn should be avoided with scrupulous care, it should be realized that even in experienced hands such a risk is greater when the X-rays are used as a curative agent than when they are employed simply as a means of physical examination. I do not, however, wish to excite apprehension in the mind of anyone, for I have had no untoward results in several hundred exposures, but only to warn all who may attempt to carry out the treatment that it is necessary to proceed with great care.

I should modify the above statement by saying that I can conceive of cases in which it may be best to push the therapeutic action of the X-rays so far that a burn is caused—that is to say, in order to get more of the beneficent action of the X-rays we accept a burn which is detrimental.

In all my cases of external cancer except one—which was without doubt a rodent ulcer—a small specimen of the growth has been submitted to a pathologist, usually to Professor F. B. Mallory, Assistant Pathologist of the Boston City Hospital. For his careful examinations and reports I desire here to express my appreciation and thanks.

The first case I will take up is that of a young man with a small epidermoid carcinoma of the lip. The growth healed, and the enlarged gland near the symphysis of the jaw disappeared after treatment. (See Figs. 1, 2, 3, and 4.)

Another patient, aged fifty years, who had been suffering for four months from epithelioma of the lip (no illustrations given), which began four years ago as a small sore, was very instructive to me. When I first saw him the lip was between two and three times as thick as usual. It was indurated, and its surface ulcerated and broken by deep furrows in which a thin, pus-like fluid had collected. The odor was penetrating, and as nearly unbearable as anything could be, but disappeared after a few exposures to the X-rays had been made; the pain was also relieved. The patient is now at work, and improvement is going on without further treatment. There is no induration, and, except shallow grooves across the lip and a small place on which a crust remains, this lip has healed.

During the treatment a portion of the chin, just under the lower lip, on which hair was growing, was exposed to the rays from time to time, and then attempts were made to pull out the hair with forceps, in order to see if it had been loosened, but it had not. This surface was thus exposed to make sure that the treatment of the new-growth was not being carried so far as to cause a burn.

A case of a typical epithelioma of the hand of a man, aged seventy-three years, indicates that we are not limited to very small growths in this use of the X-rays. This growth measured 4 x 7 centimeters. A small wart had been torn off the hand, and in five months the new growth had the proportions shown in Figs. 5 and 6. There was much induration about the ulcer. The report from the Pathologic Laboratory of the Boston City Hospital, made by Professors Councilman and Mallory, on a specimen taken before treatment by the X-rays was begun (see Fig. 7), is as follows:

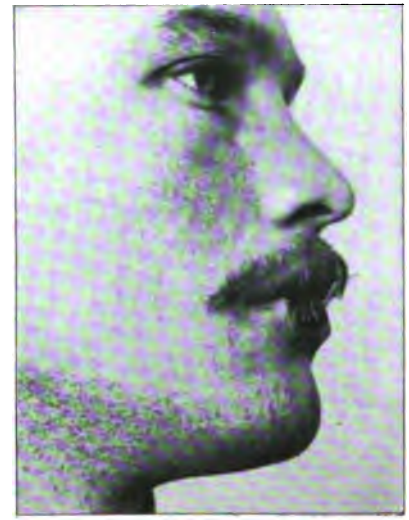
"The growth shows a typical, rapidly-growing epidermoid carcinoma containing many epithelial pearls. Mitotic figures are numerous. The surface of the growth is ulcerated; the underlying tissue is infiltrated with many polynuclear leukocytes. The carcinoma extends out at the edge for some distance in the corium, underneath the normal epidermis."

Nothing short of amputation would have been considered formerly when so large and ugly a growth was in question. It seemed presumptuous to attack it by gentle means, but as a smaller growth had yielded to this treatment it was simply a question of meeting the same enemy, although presented in a more formidable way. This case I attacked vigorously and persistently, and although it is too recent a case to be healed, yet the results thus far are satisfactory. After eight weeks of daily exposure of five or ten minutes'—sometimes of twenty minutes'—duration, the induration was largely gone and the surface of the ulcer had come down to the level of the skin, and the growth was a little smaller in size (see Fig. 8).

At this time I had a thin specimen taken, reaching down to the full depth of the growth and from the center of the ulcerated area to a point well beyond the edge of the growth into the healthy skin. This specimen was kindly examined, at my request, by Drs. Councilman and Mallory, and they reported that the central portion of the ulcerated area was entirely free from any carcinomatous growth,

FIG. 1.

FIG. 2.



Epithelioma of lip in H. N., a man twenty-five years old, before treatment by the X-rays. (Two views.)

FIG. 4.

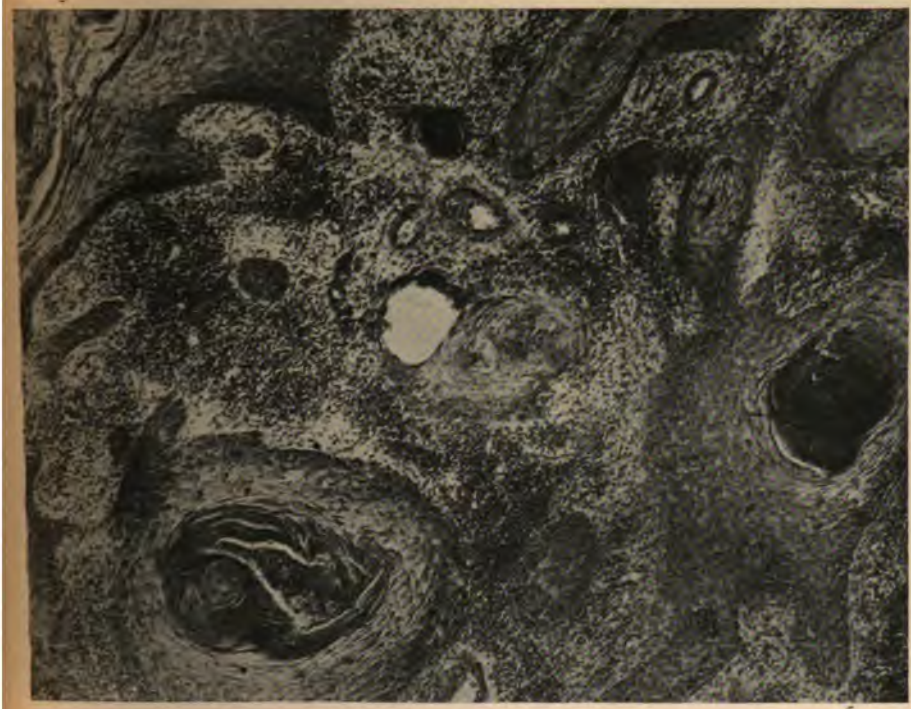
Epithelioma of lip in H. N., a man twenty-five years old, after treatment by the X-rays. (Two views.)

FIG. 5.

FIG. 6.

Epithelioma of hand of five months' duration in a man, D. K., seventy-three years old. Two views; before treatment by the X-rays.

FIG. 7.



A portion of a section through the carcinoma before treatment with the X-rays. Magnified approximately 77 diameters. The masses of squamous epithelial cells and the interstitial tissue crowded with small round cells are shown.

FIG. 8.

D. K., after some weeks' treatment. (The hand is on a larger scale than in Figs. 5 and 6.)

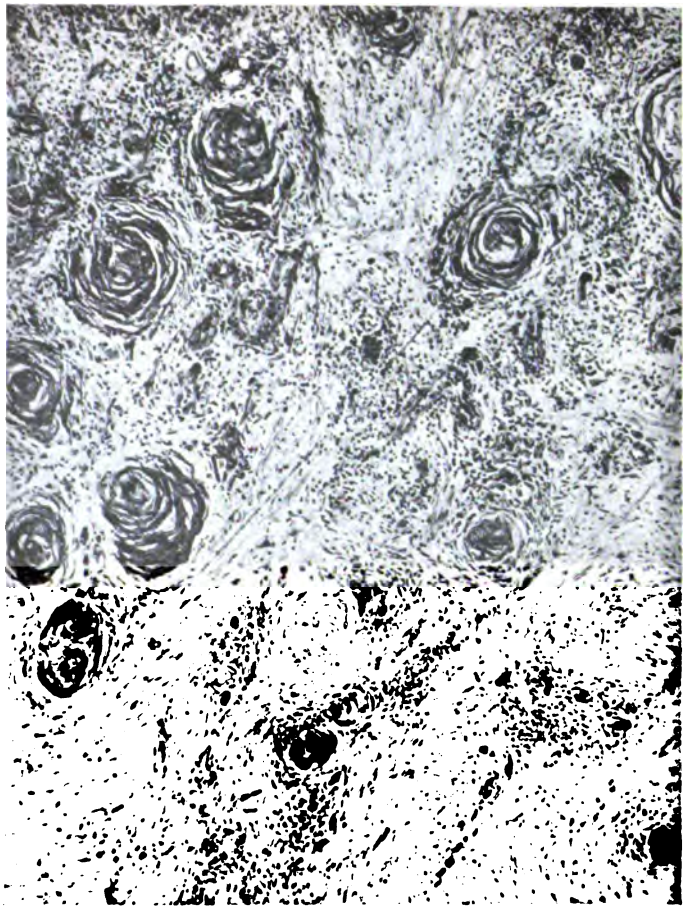


FIG. 9. A portion of the section through the center of the carcinomatous ulcer after treatment with the X-rays. Magnified approximately 77 diameters. The small groups of necrotic squamous epithelial cells and the granulation tissue in which they are embedded are shown.

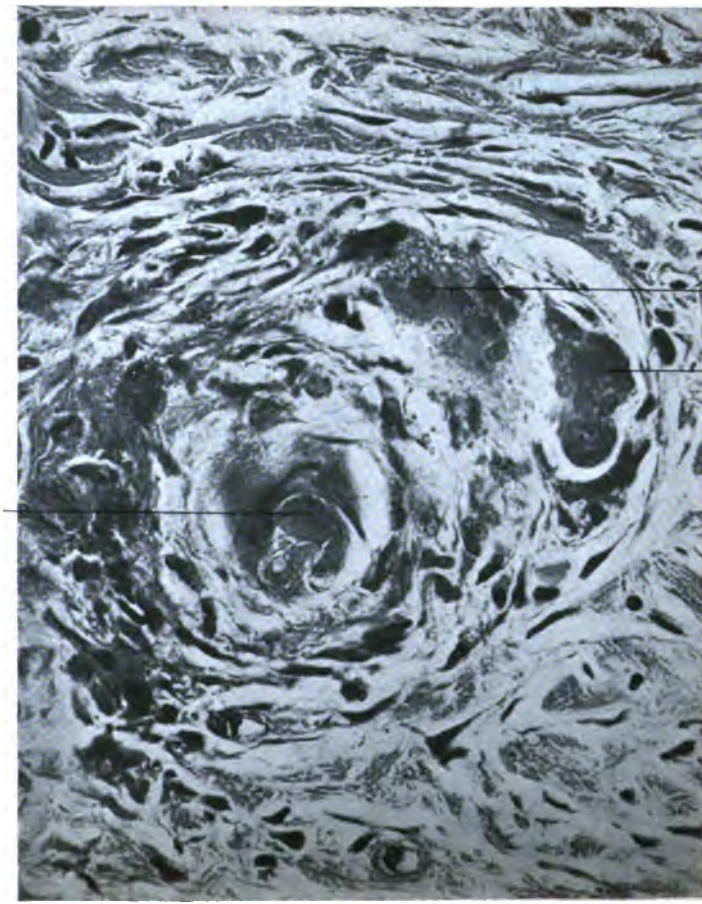
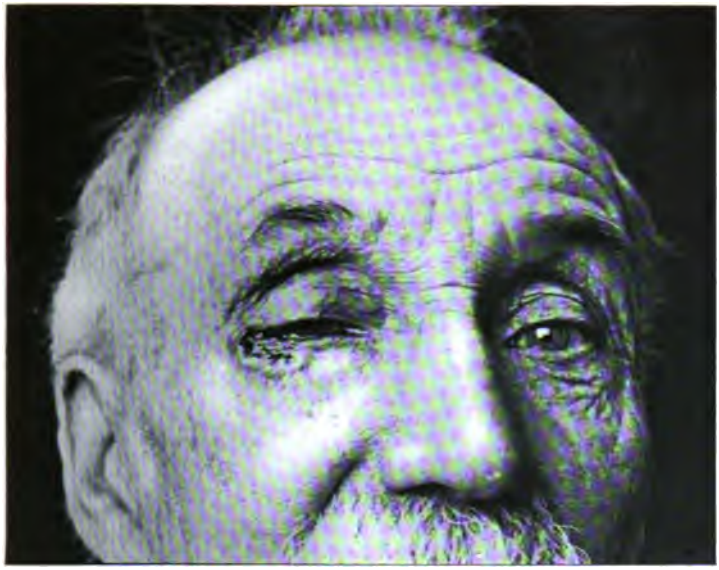


FIG. 10. A portion of the section through the center of the carcinomatous ulcer after treatment with the X-rays. Near the center of the figure is a small group of necrotic squamous epithelial cells (*a*). Around this are seen new-formed connective-tissue cells, and above and to the right are two multinucleated giant cells (*b*, *c*). The groups of necrotic epithelial cells there produce the appearance [illegible]

FIG. 11.



Epidermoid cancer of eyelid in a man aged fifty years, before treatment by the X-rays.

FIG. 12.

Epidermoid cancer of eyelid after treatment by the X-rays. There was no injury to the eye.

FIG. 13.

Rodent ulcer in a man seventy-three years old.
Duration of the disease, fifteen years.
Before treatment.

FIG. 14.

Rodent ulcer after treatment by the X-rays.

and that the whole area showed no evidence of carcinoma except at the edge near and beneath the epidermis, where a few small islands of epithelial cells, some of which were divided by mitosis, were present.

Through the kindness of Dr. J. H. Wright, who has charge of the Pathologic Laboratory of the Massachusetts General Hospital, I am able to present the preceding (see Fig. 7) and the two following photomicrographs (see Figs. 9 and 10), which Dr. Wright had made for me from the two specimens already alluded to.

The safety of the method, if properly employed, is illustrated by the following case of a man, aged fifty years, who had had an epidermoid cancer of the eyelid for ten years. (See Fig. 11.) During the past six months it had begun to grow rapidly and to ulcerate at the center. Dr. O. F. Wadsworth preferred not to operate, and sent the patient to me. Steady improvement has taken place in the growth without any injury to the eye itself, although the exposures to the X-rays were made directly over the eye, with no protection for it except closing the lids. (See Fig. 12.)

Two cases of rodent ulcer are doing well under this treatment, and one, of which a cut is shown (Fig. 13), has healed completely. (See Fig. 14.) In a third, a case of long standing, and in which the disease was far advanced, the treatment by the X-rays was interrupted in order that an operation might be done.

It is not improbable that when a cancer is of considerable size, more rapid and better results can be obtained by the application of the X-rays after an operation has been performed to remove the greater part of it.

Though I have not limited myself to the study of external forms of cancer, I will not discuss at present the results obtained by this method in internal forms. Some of these growths, such as cancer of the tongue, or parts of the uterus, can be classed among the external forms, as by the exercise of a little ingenuity they can be reached directly.

The special points that my present experience suggests may be thus summarized:

1. That this treatment causes no pain.
2. That there need be no delay on account of dread of the knife.
3. That the pain and odor are quickly relieved.

4. That healing is produced without causing any burn.

5. That the results from a cosmetic stand-point are excellent.

6. That some cases improve after a certain number of sittings without further renewal of treatment.

7. That treatment can be ambulatory, and can be carried on without the work in which the patient is engaged being given up, even temporarily.

8. Signs of improvement begin within two or three weeks.

The disadvantages are:

1. That great care should be exercised when using the X-rays as a therapeutic agent.

2. That the apparatus is expensive and difficult to use properly.

3. That the treatment must be continued for some time.

In conclusion, let me state that the work here presented in the treatment of cancer is to be regarded simply as preliminary in character. The results thus far have been favorable in every case of external cancer that has come under my care in which the treatment has been persistently carried out. The exception is the case already alluded to, in which treatment was stopped after a few sittings in order that an operation might be done. It is too early as yet to know how permanent these results will be.

To Drs. Burrell, Cheever, Wadsworth, Gavin, Monks, and Bartol, who have kindly referred patients to me, I am especially indebted.

NOTE.—In order not to multiply unnecessarily the number of cuts, I only give some of those shown at the meeting. The cuts are from my book, by permission of the Macmillan Company.

DISCUSSION.

DR. BOND: I would like to ask Dr. Williams whether he has made any experiments to determine which of the two classes of rays—the cathodal or the X-rays—does the work, and, furthermore, what effect has the interposition of a cloth between the patient and the tube?

DR. PEABODY: I would like to ask whether all of these cases were subjected to the microscope for diagnosis; and, secondly, whether they were

consecutive cases, or whether any cases treated between them did not show as good results.

DR. WILLIAMS: The cathode rays generate the X-rays, and the beneficial results arising from exposure to an excited vacuum tube are probably due to the X-rays and not to other factors.

There is no disadvantage in placing a cloth, or anything that the X-ray can easily penetrate, between the patient and the tube.

All my cases were submitted for microscopic examination except one of undoubted rodent ulcer, which is not included in this report.

Every case that I have treated has improved except one, and in this the treatment was interrupted after a short time, and was not resumed.

THEORETICAL AND PRACTICAL CONSIDERATIONS ON THE TREATMENT OF JACKSONIAN EPILEPSY BY OPERATION, WITH THE REPORT OF FIVE CASES.

By JAMES JACKSON PUTNAM, M.D.,
OF BOSTON.

THE necessity of giving advice as to the propriety of cortical excision and of operation in general, in a case of non-traumatic focal epilepsy, which came recently under my observation, has led me to review the literature bearing on this interesting disease, and to scrutinize afresh the results of my personal experience.

It is now more than a quarter of a century since Hughlings Jackson first divined the localization-mosaic of the Rolandic convolutions, and many years since Horsley, well trained by experimental research, had the courage to attempt with the knife the solution of the question whether one may argue that epileptic seizures which begin with a "signal symptom" are due to localized—possibly removable—forms of disease.

This problem is still and will, perhaps, long remain unsolved, but each new decade brings fresh data to renew the interest of the inquiry, as waves of hopefulness or discouragement succeed each other in the professional mind. Among the more recent advocates for the view that focal disease, discoverable only by the microscope, may be the cause of so-called "focal epilepsy," and that the removal of portions of the cortex containing this altered tissue and constituting the "center" corresponding to this initial symptom of the fit may, if done early enough, cure the disease, is Dr. Joseph Collins,[1] who discusses, in the autumn number of *Brain*, 1896, the histologic changes

[1] Dr. Collins expressly repudiates any desire to generalize on the basis of these cases, and it is not here intended to imply that he does so.

in two interesting cases, where thorough excision had been done by Gerster and by Curtis. A private note from Dr. Collins states that one of these patients has remained free from attacks up to the present time—that is, for six years since operation. In the first case the pia mater was thickened and adherent to the altered cortex; in the other only degeneration of the large ganglion cells was found. Collins speaks (p. 384) of this diseased tissue as having been "entirely removed;" but in regard to this point, one may be permitted to feel a grave doubt which cannot be removed by any evidence that the case has thus far furnished. And this to my mind is an important matter, because, if similar tissue has been left behind, the anatomic conditions for a renewal of the epileptic attacks still exist, and if the attacks do not recur we may have to seek the explanation in the inhibitory effects of the operation, and then the question arises whether similar effects might not have been produced by less severe measures. Certainly there is an abundance of evidence that fits may cease, or fail to occur, in spite of the presence of persistent sources of irritation.

The object of this paper is to consider some of the questions here involved, which I will state as follows:

1. Is the removal of disease-foci involving the cortex of clinical value?

2. Does the removal of the cortex itself, when apparently unchanged, add an influence of material importance?

3. How are the results of such measures as these best to be explained, and, especially, is the benefit obtained from cortical excision necessarily due to the removal either of a focus of disease or of a special "discharge-focus?"

4. What additional light has been thrown, by recent experimental researches and clinical observations, on the physiology of the cerebral cortex?

The views which I shall maintain are (1) that operations of many different sorts are of value; (2) that the beneficial action of these operations, although complex in character, is mainly due to the induction of a temporary inhibition of the morbid action of the cortex, which permits of the establishment of a more normal tendency; (3) that the removal of the apparently normal cortex is rarely advisable, and, when beneficial, acts mainly as above indicated; (4) that the cause of the persistence of the "epileptic habit" is not to be sought

alone in anatomic peculiarities of the brain, but that it shares the vitality and independent endurance of memories in general. Also, the symptom-groups which present themselves after cortical lesions conform, in general, to certain special types, which recur without being closely dependent on the localization of the cerebral injury. These symptom-groups represent, in fact, efforts at the formation of a new equilibrium on the part of a being endowed with consciousness and memory on the one hand, and with a complex brain-mechanism on the other. The principle on which this readjustment goes on in cases of actual cerebral lesion is analogous to that which is operative in "hysteria."

The points of special interest in my own cases are as follows:

CASE I. is that of a young man, aged twenty-one years, who, four years before, had suffered from a continued fever, considered at the time to be typhoid, which confined him to his bed for thirteen weeks. In an early stage of this illness, and while the diagnosis was still doubtful, his father went into his room one morning and found him unconscious. Three weeks later, while the illness was at its height, he complained one day of numbness of the hand, and almost immediately afterward became entirely paralyzed on the left side even to the left eyelid, and swallowed with difficulty. He suffered during this period from severe pain in the head, and was thought to have meningitis, but in the course of three or four weeks he could use the arm and leg pretty well, and before long all signs of disease seemed to have entirely vanished. It was six months later before indications of cerebral disorder reappeared, and then in the form of attacks of numbness of the left hand, often confined to the index finger and thumb, sometimes associated with twitching, or with irregular movements of the fingers, one after another, sometimes with a greater or less spreading of these feelings and movements to the arm and face. Only six times in all had he lost consciousness, but the numbness of the hand was sometimes preceded by a sense of fulness in the head. The leg was not much involved, but on recovery of consciousness it would feel heavy and helpless. Two or three times he had a blurring of the vision instead of the "numb" feelings, before the severer attacks, and occasionally the forefinger of the right hand would grow slightly numb instead of the left.

Operation was advised, and was done by Dr. J. C. Warren, at the Massachusetts General Hospital, June 3, 1901. A large opening having been made over the "hand-center," Dr. Warren proceeded to reflect the dura. This was found to be united to the pia by a number of firm adhesions, beside which the two membranes were separated by a dark, soft, velvety layer of tissue suggesting an organized clot, which covered most of the space exposed by the trephine opening (about two and a half inches in diameter) and extended beyond it. The affected area was in fact so extensive that the removal of the

whole of it seemed impossible, and it was more for the sake of obtaining a specimen for a microscopic examination than with a view of a cortical excision for therapeutic purposes that a small bit, about 1 cm. in diameter and 1 or 2 mm. in thickness, was snipped out with scissors from the altered pia and cortex. This was done almost at random, since faradization, even with very strong currents, had failed to excite any response. Nevertheless, immediately after the operation, the hand was found to be wholly paralyzed and the sensibility almost wholly abolished. The sensory defect involved the lower part of the forearm, but faded rapidly upward. The face also was paralyzed to a considerable degree and the leg very slightly. Trifling thickness of speech, and aphasia to the extent of forgetfulness of names, were present for a time. It is, of course, possible that these results were referable not wholly to the excision but also to the slight manipulations of the exposed portion of the brain, as well as to edema and small hemorrhages as noted by Hitzig in his experiments. But, in either case, the result affords one illustration the more of the fact that in any given area many movements may be more or less represented, and that from a given impression on the cortex certain parts will be far more affected than others; the hand, for example, more than the arm. This fact is well known, but its significance is not always appreciated. Many interesting features of this case must be passed over, but I will pause to refer to the fact that in some instances the attacks, even where the most prominent initial symptom was in the hand, were ushered in by a blurring of vision and sometimes a feeling as if the eyes were moving. As regards the further results of the operation, some improvement showed itself before the end of a week, and it was not long before the motion of the hand was regained for the most part, though there was for several years, and perhaps has remained permanently, a trifling diminution in strength and dexterity. The attacks continued for a long time much the same as before as regards frequency, but became less severe and somewhat different in character, the fingers on the ulnar side of the hand sometimes being the more affected, instead of those on the radial side, for example, beside being persistently somewhat paresthetic. The forefinger was not noticed to twitch except once or twice until six months after the operation, though paresthetic attacks were frequent. After a time his condition began to improve in every respect, and a letter received nearly six years subsequently said that he had given up the use of all medicine, that the ill turns were much less frequent, the general health good, and that on the whole he was "quite another man since the operation." Nevertheless, it should be remembered that the lesion remains, so that the improvement, however it may have been brought about, is to be laid to the score of increased cerebral resistance rather than to removal of irritation. Another letter of the present month, written just ten years since the operation, states that the improvement has maintained itself, though he is not perfectly well.

The special interest attaching to this case lies in the fact that, on the one hand, a large and persistent cortical lesion produced highly

localized and specialized seizures, of somewhat varying sorts; and, on the other hand, that a trifling injury, of indiscriminate localization, consisting in exposure of the cortex, and the snipping out of a small piece, not more than 2 mm. in thickness, induced an extensive group of symptoms corresponding to one of the several definite types such as is apt to reproduce itself from brain injuries of various sorts, not, it is true, wholly without regard to the seat of the injury, but without close correspondence to it.

The blurring of vision observed in this case was apparently due, in part at least, to a temporary strabismus. It is, however, of interest to note that the visual deficit was always referred to one side, as so often in migraine, so that one is led to recall Hitzig's discovery of a visual area in the frontal lobe.

CASE II. is that of a young girl, aged eleven years, who ever since her fourth year had suffered from fits, ushered in by numbness of the right hand and arm, sometimes to be checked by rubbing the affected parts. At the time of my examination the motions of the right hand were somewhat awkward, and the lack of development was evident, so that the case was assumed to be one of infantile cerebral disease. During the attacks consciousness was, as a rule, not wholly lost, but the face and leg were frequently involved to a slight degree. Operation was advised, and was done by Dr. Warren, at the Massachusetts General Hospital, on February 25, 1890. The dura was found strongly adherent to the pia over an area the size of a quarter of a dollar. After separation of these adhesions faradic stimulation, even with the strongest currents, failed to excite movements, except at one point, where we were able to induce twitchings about the mouth similar to those noticed during the seizures. Since it had not been possible to localize the center for hand-movements nothing further was done at this operation. The patient did very well for a time, but after a few months the attacks returned as badly as before, or worse. Another operation was therefore attempted, but the dura was found still more adherent to the underlying parts, and electric stimulation again failed to excite the cortex. It is noteworthy that although the surface of the brain was considerably torn in the dissection of the dura, no paralytic symptoms followed the operation, except slight difficulty in swallowing. The attacks were again relieved for a time, but again returned later, and this time with mental deterioration, which was progressive and necessitated the removal of the patient to an institution for the feeble-minded.

One is tempted to explain the non-occurrence of the paralysis by assuming that the exposed portion of the brain was already damaged, or, rather, that its coefficient of dynamic efficiency was low, in correspondence with the impaired use of the hand. It may well be that

this was the case, but it would perhaps involve a straining of this explanation to make it apply to cases such as those reported by Starr and McCosh, where the resection of a large piece of the cortex for focal epilepsy did not excite paralysis at all, but only a moderate disturbance of co-ordinated motion. It is to be borne in mind in this connection that similar operations upon dogs may fail to excite paralysis, although this is exceptional (Tonnini). The case reported by Sachs and Gerster, where even bilateral excision caused only a trifling impairment of function, is interesting in this connection.

CASE III.—The next patient was a man, aged thirty-three years, with an early history of special interest, partly because he had had pulmonary tuberculosis in a mild form; next because of an injury which may well have been the starting-point of his later illness. When a boy eight or ten years old, he had run while at play, headforemost and with great violence, against the projecting end of a beam, which came in contact with the left side of his head near the vertex. He was knocked senseless by the blow, but seemed after a time to have recovered without permanent injury. Within about two years of this period the first symptoms of his present illness showed themselves in the form of recurring attacks of "prickly feelings" in the thumb, forefinger, and middle finger of the right hand and the adjoining portion of the palm. Sometimes, also, the right side of the face, in the parts adjacent to the angle of the mouth, would be involved, and the right half of the tongue. Occasionally the attacks would begin with paresthesia on the inner surface of the upper arm, about midway between the elbow and the shoulder, and would spread thence both up and down the arm and to the adjacent portion of the chest (area of distribution of nerve of Wrisberg?) and the attacks beginning in this way were the ones most likely to terminate with face and tongue symptoms, and were, therefore, the most dreaded. With slight variations in type the attacks recurred at short intervals, rarely a day passing without one or more of them. Indeed, their frequency had gradually increased, but the tongue was less often involved than formerly. Occasionally, though rarely, these paresthesias were attended with clonic spasm, or flexor cramp, of the fingers and even the arm, of moderate severity. The first occurrence of this sort was in 1896, and in the three years following it was repeated five times. Twice only, both of the times being on the same day, he had a loss of consciousness, preceded by a severe jerking of the arm and by a painful feeling as of a series of blows, delivered successively at higher and higher levels from the neighborhood of the hand to near the shoulder. It felt, he said, as if the arm were being chopped off in segments with an axe or by machinery. On two or three occasions, also, a temporary embarrassment or even loss of speech had occurred, generally in the early morning. The attacks in the hand repeated each other with great accuracy. The first sign would be a stinging sensation in the end of the thumb; this would

be followed by a similar feeling at the end of the forefinger; and then by a sensation as of something darting down the length of the forefinger, then along the middle finger and into the radial portion of the palm of the hand. Finally, the face near the mouth would be involved.

My first examination, in August, 1898, revealed a very slight paresis of the right side of the face, a slight but definite impairment of cutaneous sensibility over the palmar surface of the thumb and forefinger, as tested by light contact and pricking, and a slight awkwardness in the use of the fingers, as in buttoning the clothes. The sensibility of the right side of the face was affected similarly, but to a less degree. There was no considerable gross weakness of the hand, except for a time after each attack.

Although these paresthetic seizures did not incapacitate the patient for work, yet they harassed him greatly, and he readily consented to the idea of an operation, which was, however, not performed until December 15, 1899, on account of the presence earlier of slight tubercular signs in the lungs. By the time of the operation these signs had disappeared and no bacilli of tubercle could be found.

The operation was performed by Dr. J. C. Warren, at the Massachusetts General Hospital. A large trephine opening was first made over the Rolandic convolution, but nothing abnormal was seen until the dura had been reflected, when the pia toward the anterior part of the space was found to be opaque. The opening being enlarged in that direction a tough adhesion of the size of a knitting-needle was discovered, uniting the pia and the dura together. This was excised, together with a small bit of the cortex, Dr. Warren having first assured himself by a careful exploration with the probe that the surface of the brain for some distance around was free from similar lesions. It may be stated here that a subsequent microscopic examination of the excised piece, by Dr. W. F. Whitney, confirmed the view which the appearance of the parts had suggested, that the changes were due to inflammation, not to new-growth.

The recovery from the operation was satisfactory in all respects, the skin-wound healing by first intention.

An intensification of the numbness in the fingers, and of the impairment of tactile sense, and the extension of these signs to the ulnar distribution, which was manifest immediately after the operation, together with an increase of the facial paresis, indicated that the neighborhood sought had been reached, though it cannot be affirmed that the whole lesion was removed. The opacity and edema of the pia, slight as it was, would indeed suggest a wider extension of the cortical irritation.

On the second day following the operation he had a bad attack of numbness, with cramping of the hand, then two days passed without attacks. During the following two weeks the numbness recurred more frequently than before the operation, but without much cramping, and with a tendency to lessen. The facial paresis soon became less, and a paresthesia of the tongue and gums on the right side, associated with a hesitation in speech, which

were all considerable just after the operation, had almost disappeared by the end of the third week.

In the two years which have elapsed since the operation the attacks of numbness have recurred about as before, and there has been in addition an almost continuous paresthesia of moderate degree, not exclusively limited to the median nerve distribution. The left foot has also become the seat of occasional sensations of similar sort—referred especially to the joints of the toes[1]—and the same feeling has been present in the right side of the neck.

It is worthy of remark, as recalling the observations of some of the cerebral physiologists who found that the tendency of cortical irritation to produce epileptiform spasm could be intensified by gentle stroking of the limb, that this patient has at times noted a recurrence of the numb seizures when the ends of the fingers were rubbed or knocked. Yet, strangely enough, it was not possible to produce this result at will, the admixture of conscious volition seeming to exert a sort of inhibitory effect. Before the operation it was only the end of the thumb which acted in this way as an epileptogenic zone, but since then the same peculiarity has been shared by the ends of some of the fingers.

Cases of "Jacksonian" epilepsy of various types have been so often reported as to be thoroughly familiar, and the fact is well recognized that one has no right to infer a limitation of the lesion or disease-process to the cortical area corresponding to the "signal symptom." Sharply localized epileptiform outbreaks occur with tumors of considerable size and even in "idiopathic epilepsy," and this occurrence seems to indicate no more than that a certain cell-area is abnormally unstable, whether on account of disease or from an inherent excitability due to the nature of its functions, as in the case of the areas corresponding to the mobile hand and speech-organs.

In correspondence with this is the interesting fact, well illustrated by the present case, that the irritation due to a given lesson may induce multiple or alternative results, represented here by the occurrence, now of the thumb-numbness, now of the upper-arm-numbness, as the "signal symptom." The plausible explanation is that the corresponding cortical areas are particularly irritable, so that a dis-

[1] In Case I. the hand of the side opposite to that usually affected was involved occasionally, even alone.

charge may easily start in them with sufficient force to act as a vortex center.

The resemblance of this case to Case I., especially as regards the paralysis after operation, yet with a lesion of far less extent and severity, is also obvious.

CASE IV. is that of a boy whom I had the opportunity of watching for a long time before the operation, which was done by Dr. Keen, of Philadelphia, and have had under observation ever since. He had had from early childhood frequent attacks, of short duration, and not always attended with entire loss of consciousness, in which his head would turn to the right and make a rapid series of nodding movements, while the right shoulder would rise and fall rapidly. The right arm was also more or less involved. Severe or general convulsion did not occur. There was no reason to suspect localized disease of the cortex, but the prominence of the shoulder movements suggested the hope that excision of the corresponding part would be of some avail. Localization was carefully done on the skull, and afterward, successfully, by faradization of the cortex, and the corresponding portion was then excised by Dr. Keen. A temporary weakness of the arm followed, but the epileptic attacks went on much as before, though somewhat changed in character, and all that can be said (which is perhaps a good deal) for the effects of the operation is that from that time the signs of the disease have been somewhat more manageable by bromides and other treatment.

CASE V. is that of a young man, aged seventeen years, of excellent habits and good previous health. His previous history shows nothing that would explain the present symptoms unless that he had a very severe whooping-cough when four or five months old, and that, having been fond of athletic sports, he had received a number of severe blows on the head, though not such as apparently to cause permanent injury. For the past two years he had grown very rapidly. During the past year he had become gradually aware of prickling sensations in the left hand and fingers, recurring from time to time and lasting about fifteen seconds. During these times the sensibility of the skin would become heightened, so that a rough object would feel still more rough, etc., while at the same time the hand would lose its strength. There had been no impairment of consciousness until three weeks before examination, when he had had two convulsions in one night. Since then the numbness of the hand had become worse, so as to be actually painful, and the fingers would become cramped in a position of extreme extension, the thumb being drawn in upon the palm of the hand. The pain was usually confined to the last two joints of the index and middle fingers and the end of the thumb.

Without entering into further details, I will say that after a thorough bromide treatment, under which the attacks remained absent for a number of months, again recurring, however, at the end of that period, it was decided

to operate, in the hope that some cause of local irritation would be found as in some of the other cases.

The operation was done by Dr. Warren in February of the present year, a large skin and bone flap being turned back and the dura incised and reflected. The cortex presented an absolutely normal appearance, and nothing more was done than to palpate for underlying tumor or cyst. As a result of this manipulation, or of the simple exposure, a well-marked paresis of the hand came on, with impairment of sensibility in all modes, including the sense of position and the stereognostic sense, and also a slight drooping of the left side of the face. These conditions were exactly like those which were reported as following operation in the preceding cases, but less severe, and not more lasting. Only five months have elapsed since the operation was done, and I report the case only for the sake of completeness and the interest of the diagnosis. In fact, however, the feelings in the hand have been much less frequent, thus far, and no severe attacks have occurred. He is on a thorough bromide treatment, which it is planned to continue for a long time. The only way in which it would have been possible to differentiate this case, where no gross lesion was present, from those where localized meningitis was found, would have been by the entire absence, before operation, of any trace of permanent impairment of the functions of hand, which in the other cases was present, though to a very trifling extent.

CASE VI.—I wish finally to report the final history of a very interesting case reported by Dr. A. T. Cabot,[1] in conjunction with whom I had the opportunity of studying it. The pathologic diagnosis, which could not be made with positiveness before the operation, was a large, subcortical cyst, believed after examination to be of traumatic origin. The original "signal symptom" was a paresthesia of a certain area on the right thigh, but later the very interesting sign showed itself of a paresis or even paralysis of the leg, and sometimes the arm and face, coming on at times as long as fifteen minutes after the initial symptoms had passed away. Loss of consciousness was comparatively rare.

A thorough and continuous draining of the cyst seemed to lead to its filling up and obliteration, and attacks became slight and rare, so that the patient felt able to marry and to engage in active and responsible occupations, which he managed for several years. News has, however, recently reached Dr. Cabot that the attacks returned some six months ago, and still more recently that he had suddenly died.

It is noteworthy that the "signal symptom" in this case was, as a rule, a numbness over a portion of the thigh, instead of over the hand or foot, as is the rule, though the lesion was of such large size as necessarily to involve extensive areas. It is also of importance, as illustrating the occurrence of psychic phenomena even with these

[1] Boston Medical and Surgical Journal, 1897, vol. i. p. 233.

localized lesions, that the patient would sometimes jump up and laugh or show odd behavior for a moment as the sensation was first felt. Such acts recall the familiar cases where a dream is initiated by some slight excitation, such as a knock on the door, yet develops in such a way that the noise seems to form the last stage of the process instead of, as in fact, the first. It may be readily conceived that the psychic portion of the attack might, on some subsequent occasion, initiate the process in its turn.

To return now to the consideration of the questions specified at the beginning of the paper, it may be stated, as a fact which would probably be generally admitted, that operations for the relief of focal epilepsy, whether these aim at the removal of local sources of irritation or of diseased areas involving the cortex, or of the removal of the apparently normal cortex, are often unquestionably of great benefit, although they have not accomplished nearly all that was hoped of them. Not to speak of special cases and groups of cases, some of the best of which have been contributed by American physicians, this statement is substantiated by several recent and careful compilations of German surgeons, as Braun,[1] Graf,[2] and Matthiolus.[3]

When it comes to the important question of the *comparative* merit of cortical excision, as against operations of less magnitude, such as simple exposure of the cortex or loosening of dural adhesions and the like, which sometimes have an extraordinarily favorable effect, the case is not so clear, especially when it is remembered that the excision is likely to cause lasting inco-ordination of slight degree, and that the resulting cicatrices may be by no means indifferent for the health of the surrounding parts[4] of the brain.

Still, the figures cited by Matthiolus, taken for what they are worth, indicate rather better results from operations in which the brain has been included in the operation than where only lesions of the brain coverings have been treated.

"Cures," *i. e.*, for example, a cessation of fits for five years, have been very few in number, and although such a case as that of Collins

[1] Deutsch Zeitschr. f. Chir., 1898. [2] Arch. f. Chir., 1898.

[3] Deutsch Zeitschr. f. Chir., 1899. Such compilations have, to be sure, only a limited statistical value, since the grounds for a valid classification and comparison of the different cases are very imperfect. The study of individual cases is really of greater value.

[4] See McCosh, American Journal of the Medical Sciences, 1898, vol. cxv. p. 549, and other writers.

and Gerster's is very impressive and encouraging, where six years have elapsed during which, after cortical excision but under continual bromide treatment, no fits have occurred, it is to be remembered that in the first case of the series reported by McCosh an equally good result followed simple trephining, separation of the adherent dura from the roughened bone, and the removal of bone-fragments, although there can be little doubt that the broken adhesions instantly reformed, so that the local conditions of nutrition probably remained in the end unimproved.

The conclusions which seem to be most reasonable on the other points are the following:

Epilepsy of the "Jacksonian" type is usually set up, in the first instance, by gross sources of irritation, either peripheral or central, but for the most part external to the brain tissue itself. Yet there is probably one form which has the same pathology, with so-called idiopathic epilepsy of more common types.[1] The anatomic changes found under these circumstances are to be regarded as usually either secondary to the convulsions or else as indications of an abnormally developed brain. Perhaps uremic and other toxic convulsions of focalized type should be classified with this group, inasmuch as the poison is distributed through the brain as a whole, and the localized effect is not to be sought in the localized cause.

It is doubtless true—as Sachs[2] and Collins[3] have pointed out—that in some cases of Jacksonian epilepsy degenerative changes may be found in excised pieces of the cortex which were not recognizable to the naked eye. On the other hand, however, the evidence that these changes are of a kind likely to excite epileptic seizures seems to me insufficient, and it is especially improbable that lesions of such a character would be limited to a small area of the cortex to such a degree as to be entirely removable by operation.

Not only is the existence of such changes in the form of circumscribed focal lesions improbable, but if they existed we have no clinical criteria by which to delimit them before death. To take, for example, the most common type of Jacksonian epilepsy, that which

[1] See the report of a case with apparently negative findings, by McKendrick. Brain, Autumn, 1899.

[2] American Journal of the Medical Sciences, 1896.

[3] Brain, Summer and Autumn, 1896.

begins with sharply defined hand-symptoms, there are large numbers of cases to show that the lesion, when gross, may be of great or indefinite size, and may vary greatly in position with relation to the so-called hand-area of the cortex. If then a large tumor or cyst or a patch of diffuse meningitis may cause sharply localized symptoms, why should not the same be true, *a fortiori*, where the lesion is a diffuse degeneration of ganglion cells?

Again, it is by no means certain that, in the fit of the Jacksonian type, the morbid cycle, of which the convulsion is the most obvious feature, always begins with a "discharge" at the point corresponding to the signal symptom. If we bear in mind the analogous case of a purposive movement, as when, for example, we put out the hand to grasp some object, or clinch the fist in obedience to some emotional impulse, we must admit that these movements are preceded by a series of cerebral events of the details of which we are largely unconscious. In a similar way a Jacksonian attack may represent the terminal stage of a complex cerebral action as well as the initial stage, and the persistence of the "habit" may be due to a persistence of a *memory*, more or less independent of the brain.[1] This reasoning would apply, of course, more especially to the Jacksonian types of idiopathic epilepsy, but there is room for question whether it does not apply, in some measure at least, to the cases of localized lesion as well, especially where a good many attacks have already occurred. Thus in Case I. of this series, the hand-fits, although they were sharply localized, even to the thumb and fourth finger, as a rule, and sensory in character, were often preceded by blurring of vision of strange feelings in the head. Everyone has been inclined to admit that the longer the time during which the seizures due to localized irritation occur, the more widely the brain, as a whole, becomes involved, and although it has been amply proved that even after twenty years and more a suitable surgical operation may, in favorable cases, arrest the epileptic tendency, yet it is also pretty certain that the co-operative action of ever-widening areas of the brain, or even of the brain as a whole, may show itself almost from the very outset, and this especially in children. When this result has been reached the case of the patient with traumatic or focal epilepsy probably differs but little, if

[1] Bergson. Matière et Mémoire.

at all, from that of a patient with idiopathic epilepsy. In other words, the epileptic tendency in his case has become one of the regular modes of activity of the whole brain, and the destruction of a single part, the hand-center, for example, if it checks the seizures, must do so through some influence such as we are apt to classify as "inhibitory." If the gathering tension which precedes the epileptic outbreak had been in the habit of expressing itself through some motion or sensation of the hand, the tendency to this same mode of expression is likely to remain even after mutilation of the cortex, though susceptible of being checked at its source by inhibition or otherwise. If the fits go on, however, the motion or sensation which occurs after the destruction of a given center is likely to be more coarse in character and less sharply limited in extent than it was before that part of the delicate mechanism of the cortex had suffered damage.[1]

In advocating the importance of the "inhibitory" and formation-of-new-habit theory of surgical operations in Jacksonian epilepsy, as against that which refers the benefits obtained to the removal of disease-foci, I do so not as maintaining that the former explanation is perfectly satisfactory or intelligible, but only that at the present moment it is the best one available. It has also the advantage that its provisional adoption encourages us to study and classify the cases of benefit from operations of other sorts, instead of passing them by with a shrug, and may thus lead to more profitable modes of treatment of analogous sorts.

As a step in this direction, the fact deserves mention that Eulenburg[2] in his interesting discussion of some of these points in 1895, in connection with the report of a case where the epileptic attacks held off for three years after a cortical excision, and then returned, has a good word to say for the striking observations of Wetterstrand on the treatment of epilepsy through hypnotic suggestion. This mode of treatment is theoretically justifiable, since it is as reasonable to believe that epilepsy may be influenced as favorably by one sort of mental attitude as that it may be influenced unfavorably by another, and the latter has always been accepted as a true sequence.

The natural history of all the neuroses and psychoses is indeed

[1] Chipault. Traveaux de Neurologie Chirurgicale, April-July, 1900; abstract in the Journal of Nervous and Mental Disease, April, 1900.

[2] Eulenburg. Berlin. klin. Wochenschr., 1895.

marked by a tendency to the occurrence, under favorable conditions, of periods of cessation of symptoms. Tic douloureux and migraine are cases in point, but there are many others. There is such a thing as temporary "set" or "cyclic" action in the nervous functions analogous to the vortex-tendency, which sets up the ever-forming and dissolving eddies on a swift stream. These temporary inertia—or habit—vortices may work for good or evil, and it is on the possibility that the formation of one tending to good may be encouraged that a large part of the hopefulness of therapeutic endeavor is based.

It is possible, of course, that the manifold operations which have been done for epilepsy, and have been attended with a considerable measure of success, sometimes do good in one way, sometimes in another. But the mind instinctively and justly seeks to cling to a single explanation as long as possible, and it would be fair to urge that if the excision of the apparently healthy (even though really slightly diseased) cortex effected its results on a wholly different and more rational principle from other operations, these results would be distinctly better, which, in fact, they do not seem to be.

It is common to see the inference drawn that because the cessation of certain clinical symptoms follows a given therapeutic measure, therefore the cause of the symptoms has been discovered. This is the diagnostic argument *ex juvantibus*, and it reappears in a thousand forms. In fact, this reasoning is misleading and fallacious. The morbid cycle of disease, especially if this takes the form of a neurosis, whether epilepsy, asthma, Graves' disease, or any other, may often be broken in upon and dispelled by influences and impressions which had nothing to do with its formation, and this is another justification for the doubt whether a cessation of fits following an operation for excision of a supposed disease-focus in the cortex proves, or even strongly indicates, that we thereby remove the original cause of the disease. I would remark, in passing, that the presence of the localized meningitis discovered in three of the above cases, as in several others which are on record, not to speak of that which had developed (possibly as the result of meningeal hemorrhage) during the typhoid fever, in Case I., seems to me of distinct clinical interest. It is not commonly accepted that this lesion is apt to follow such injuries to the head as these patients describe, or to occur from such illnesses as those from which they had suffered.

Reasoning from the considerations above stated, I believe that the arrest of epilepsy through surgical operation is an affair primarily of inhibition, and next of the establishment of a new habit, made possible by this temporary arrest of the morbid outbreaks. I do not believe that it is necessary to look for a focal lesion to account for focal symptoms any more than it is necessary to look for a focal lesion to account for the numbness of the hand or the hemianopsia which usher in an attack of migraine.

If this reasoning is correct, the therapeutic problem is how best to secure this inhibitory action. Cortical incision may be the most effective means to this end; but it sometimes leaves the patient with an embarrassing and persistent awkwardness of movement, and should therefore not be undertaken if other means will serve which are not open to the same objection. Clinical observation and laboratory experiment seem to indicate that even a simple exposure of the cortex may damage its nutrition enough to cause temporary paralysis of sensation and motion in many cases, yet without inducing permanent impairment of function of serious amount, and anyone who will take pains to look over a large number of important cases will see that not only the moderate degree of success observed by Dr. Warren and myself, but occasionally a much greater degree is obtainable in this way. The cause of the temporary disturbance of motion and sensation which follows simple exposure of the cortex is attributed by Hitzig to the occurrence of punctate hemorrhages deep in the cortex, and to edema and anemia of the brain, partly resulting from its being pressed into the trephine opening by the uncompensated action of the cerebral circulation, the counter-pressure of the cerebral spinal fluid in the subdural space having been removed. This counter-pressure may, he thinks, be re-established if the excised bone is replaced in its old position, as by the Wagner bone-flap method of opening the skull for operations of this sort, which is now so common. Even with this precaution, however, it is probably a long time before the circulation and nutritive conditions in the exposed cortex become normal, if, indeed, this ever happens.

An advantage of this operation of simple exposure of the cortex is that it can be repeated if necessary, and that it does not shut out the possibility of doing excision of the cortex later. But whatever operation is done it should, in my opinion, be considered that the arrest

of the symptoms is mainly useful as affording a better opportunity for bromide medication, and this opportunity should be taken advantage of energetically. It is not necessary to consider here the details of the bromide treatment, but, in fact, I believe that the best method is that originally proposed by Charcot and recommended by Tourette in a recent paper, according to which the dose is increased for three weeks, then dropped to the starting-point, and then increased again, and so on. The bromide treatment should also be reinforced by every hygienic influence that can be devised.

As regards the question of the physiology of the cerebral cortex, the tendency of the more recent researches has been, on the whole, confirmatory of the generalizations of Goltz, and we must now cease to regard the cortex of the brain as a mosaic of specialized centers, and consider it rather as a network, standing as the expression of closely interdependent functions. Furthermore, real light has now been shed upon the vexed question of the relationship between consciousness and the brain, and upon the part which each plays in producing the phenomena of life and disease. In confirmation of these statements, I will refer to the investigations and interpretations of J. Richard Ewald,[1] of Loeb,[2] of Hitzig,[3] and of the psychologist, Bergson.[4] Ewald managed to arrange the conditions of his experiment in such a way that the surface of the brain of dogs could be excited here and there long after the shock of the first trephining operation had passed away, and while the animals were running about in perfect health and indifference. Under these circumstances he found it possible to excite localized movements of various sorts by electric stimulation at points quite removed from any corresponding "center," and he points out that, in fact, arrangements *must* exist for uniting closely the functions of such a part as the hand with those of the eye and ear, as well as the touch. He shows that the strong tendency toward recovery from the effects of local destruction of the cortex ordinarily implies the preservation of the semicircular canals in the labyrinth, and that where these have been removed the recovery is incomplete or does not occur. These facts are best explained, he believes, under the view that the semicircular canals have the function

[1] Verh. des Cong. f. Inn. Med., 1897, vol. xv. p. 245.
[2] Physiology of the Brain, Chicago, 1900.
[3] Arch. f. Psych., etc., 1900.
[4] Matière et Mémoire.

of maintaining a general muscular tonus, and that this provides a sort of compensation for the loss of the tactile (or mainly tactile) functions of the Rolandic convolutions, like that obtained through the action of vision in tabes.

The cortex of the brain is a great network, an immense telephone switch-board, by means of which the individual seeks, as best he can, to place himself in active relations with his environment. The sense of his desires and needs in the way of recognition and expression is a possession of his whole being, and a possession which he will struggle hard to maintain, and which cannot be excised through mutilation of any small portion of the cortex. If you damage his switch-board at one point you may make it more difficult for him to accomplish certain results, but unless the damage be too great, accomplish it he will, if only in a roundabout fashion, by a process of readjustment which will begin to assert itself as surely and as promptly as that which makes the epidermis begin to grow again upon the abraded skin. It is reasonable to suppose that the hand-center is also a center, in a feebler degree, for the arm, the face, the shoulder, and the leg, and it is fair to suspect, although the fact has not, I believe, been proved, that if a sufficiently delicate test were employed, it would be found that even feeble electric excitations of this area, like movements of the hand itself in health, would be attended by feeble contractions of the muscles which fix the root of the limb. And, conversely, after excision of the apparent hand-center, the readjustment which asserts itself forces the mechanism which had previously been correlated principally for coarser movements of the arm to substitute itself for that which had been destroyed. It is certainly true, to use the term employed by Loeb, that the problem of the cerebral activity is one that is rather dynamic than anatomic. It is like the case of a quantity of water which has stood in a complicated system of tubes, gradually finding a new level when one of the tubes is taken away. The dynamic excitability, if the expression is permissible, of the parts next related to that which had been previously in use, needs only to be raised to the necessary point, for the old processes and functions to go on as before, at least after a fashion. The case is more or less like that of aphasia. It is true, namely, as Hughlings Jackson long ago pointed out, that, underlying the bizarre variations of the speech disturbance in different forms of aphasia, there is always a tendency

toward a readjustment of the language function, of such a kind that this function is found at the end not to have been mutilated in parts so much as weakened as a whole. In the struggle for the re-establishment of a new equilibrium the *verb*, which expresses action and has a wider hold on the individual's life of relation to his environment, will always be recovered first. The proper names, which stand alone, will be recovered last.

In other words, if the individual can no longer present just the same front to the world as before, he will, nevertheless, present, so far as possible, the same *sort* of front.

It is interesting and important to note that this principle which underlies the readjustment of the cerebral functions, after injury or disease, on a plan modelled on the conditions of health, is essentially the same with that which underlies the readjustments in the case of the hysteric patient, only here the process is seen in an exaggerated, often grotesque form. Take, for example, the case of the anesthesias of cerebral origin. The modern French view has recently been expressed with admirable clearness by Verger[1] that in all cases where complete hemianesthesia is present this is to be regarded as a sign of hysteria, though perhaps grafted on to the symptoms of an organic lesion of the brain. On the other hand, the anesthesia to which a structural lesion of the brain gives rise in its own right—*i. e.*, when uncomplicated by hysteria—does not, he thinks, occupy one whole half of the body, but only the extremities, where it gradually increases in intensity toward the distal end. I desire now to point out that, although these peculiarities of distribution are doubtless of clinical importance, yet the two conditions, which we call, respectively, hysteric and organic, resemble each other in the respect that neither of the forms of readjustment of the sensory functions seen in them proceeds on anatomic lines, but both are examples of the re-establishment of an equilibrium for functional ends, for the benefit of the individual as a whole. It is, again, an affair of dynamics, and not of anatomy alone.

Just as in aphasia a patient is apt to lose his isolated names first and to retain his verbs the longest, so when his sensorimotor cortex is injured he retains the more fundamental use of his limb and loses the luxury functions of the hand and sometimes the sensory functions

[1] Arch. Gén. de Méd., November and December, 1900.

which are associated with the motor functions of this type. I maintain that this is precisely the ground on which the hysteric patient is supposed to lose and to retain, as the case may be, the sensory functions of his skin and special senses. There is a difference between the two sets of cases, but the underlying principle of readjustment is the same.

It is a merit of this mode of regarding the brain functions in disease that it brings out the dynamic, self-adjustable, so-to-speak "fluid" properties of that organ, and contradicts the tendency to represent it as an inflexible mechanism. It contradicts also the erroneous theory of the "storage of memories in the cortex,"[1] subject to being destroyed piecemeal by disease. It is just because memories exist, in a certain sense, independently of brain action, that they cannot thus be destroyed, and that the marvellous readjustment of the functions of the damaged brain on the old lines of health is able to occur.

It is also of interest to note that Hitzig believes, on the basis of a long series of experiments, that he has demonstrated the existence of a visual center in the frontal lobe, of analogous significance to that in the angular gyrus. Thus provision is made for movements of the eye and for vision in two widely different portions of the brain. Neither of these centers seem to be, according to Hitzig, primary centers of vision; both stand in a similar relation to some more fundamental visual area.

DISCUSSION.

DR. JACOBI: If there is any form of epilepsy that in my opinion is not susceptible to suggestive influences it is the Jacksonian type. There we expect to find a local cause, and it should be less susceptible to such influences whether we find an anatomic cause or not. It did not appear to me that Dr. Putnam was very partial to operations compared with what I have heard other neurologists say about them. Still, it has also occurred to me that of late years operations for Jacksonian epilepsy are made in smaller numbers; what impresses me most is that so frequently nothing is found at the operation. In the last few years I have had two autopsies made carefully where the symptoms had been those of Jacksonian epilepsy, but absolutely no local

[1] Compare Bergson, Matière et Mémoire.

lesion was found. It seems to me that operations do not appear to be so promising in these cases as they were believed to be in former years.

DR. SACHS: I think it is evident that those interested in the subject have become a little more conservative in regard to advising these operations, but they can hardly be censured for that, since it is due to a closer study of the subject. We can all fully indorse the position taken by Dr. Putnam, that Jacksonian epilepsies are the only ones that should be operated on, and in those operable cases I would like to urge that if the operation is to be done it should be done at the earliest possible moment. The vast majority of Jacksonian cases I believe are due to focal lesions that may be macroscopic or microscopic, and, in answer to Dr. Jacobi, I would say that even if there should appear to be no gross lesion you cannot determine that no lesion exists until a very careful microscopic examination has been made.

I would also like to mention the fact that one of the very earliest cases I operated upon was one in which the lesion was revealed by such microscopic examination, and I am also able to report that the first recurrent epileptic attack was more than eight years after the operation. I think that operation was more than warranted, for the patient was at the time in the way of becoming a confirmed epileptic, whereas he has now been able to maintain himself by his own efforts for more than eight years.

DR. PUTNAM: I should not like to put myself on record as not favoring operations, for even in the cases such as Dr. Jacobi has spoken of, I think an operation might have done what I suggested in my paper, viz., have produced an inhibitory effect upon the attacks. I agree with all that Dr. Sachs said except as to the finding of a focal lesion in the region corresponding to the attacks. I do not believe that these diffuse lesions are to be classed as focal.

THE TOXIC ORIGIN OF NEURASTHENIA AND MELANCHOLIA.

By M. ALLEN STARR, M.D.,
OF NEW YORK.

WHILE the interest of the physician is commonly excited by rare and unusual cases rather than by the common run of disease, it is after all the ordinary light type of case which comes most frequently under his attention and demands his effort. There is no need to affirm the frequency of mild cases of neurasthenia and of melancholia, inasmuch as every practitioner sees such cases constantly. The complaints of a neurasthenic are so numerous and the general frame of mind of these patients is so depressing, that the disease fails to elicit very much interest on the part of the practitioner, or of the neurologist to whom in despair he often refers these cases. Yet it is my experience that a little care in their examination often enables one to classify them into a variety of different types, not only cerebral, spinal, and vasomotor types, but also into different classes according to the origin of the disease. Thus one can recognize clearly cases that are due to anxiety and worry; cases that are due to overexertion, mental and physical; cases that are due to beginning degeneration of the neurons, destined to go on to organic disease; and lastly, cases that are distinctly toxic in their origin. It is to the latter class that I wish to direct attention at the present time.

I do not wish to delay you by any long study of the symptomatology of this variety of neurasthenia. It usually occurs either in poorly nourished women, or in men about the age of forty-five who have lived rather freely, have taken little care of their diet, and have indulged in the use of alcohol and tobacco, and who have neglected exercise.

The chief symptoms in this form of neurasthenia are headache, dull pressure in the head and back of the neck, sensations of fulness in the

head, with inability to concentrate the attention, irritability of temper, manifest irregularities of the circulation shown by cold extremities, and by frequent flushings and burnings in different parts of the body, and general disorders of the digestion, either of the nature of acid dyspepsia, or of considerable evolution of gas in the stomach and intestines, with irregular and very offensive stools. In these cases the urine is irregular in quantity, at times scanty, of high color and of high specific gravity; at other times profuse, light, and of low specific gravity, and at all times it contains large quantities of indican or indoxyl. In this condition a mild state of melancholia is very frequently associated with the neurasthenia, and in almost all cases of mild beginning melancholia the same symptoms are present.

The chief characteristic of this type is the alternation of feelings and symptoms at different times of the day. One can draw a curve representing the intensity of symptoms in these patients with remarkable accuracy, a depression in the curve representing the depression of spirits and intensity of suffering. From noon such a curve rises gradually toward the normal level. At 9 P.M. it begins to descend; during the night it falls to its lowest level, so that at 4 A.M., when these patients commonly awake, they are in the deepest distress of mind and are suffering the greatest discomfort of body. For a period of three or four hours the curve is then at its lowest point, but by breakfast time it begins to rise and continues to rise slowly until the normal level is almost reached at noon. This cycle of misery and well-being is so constant and so uniform that patients themselves readily recognize it. It is perfectly evident that a variable condition of this character must be produced by a varying intensity of cause, and the fact that the maximum of distress occurs in these patients after the sleep of the night is an indication that it is not the wear and tear of exhaustion which produces their chief symptoms. It must be some toxic agent which accumulates in the blood during the period of sleep, which reaches the point of irritation early in the morning, which is counteracted by the activity of the day, and hence is less intense in its action toward afternoon. That this toxic agent is manufactured either in the intestines or in the stomach seems to be the most natural theory, inasmuch as activity in the digestive process appears to aid in the elimination of the poison. Exactly what this toxic agent is I do not know. As already stated, I find that indican

or indoxyl is the one particular thing found in the urine in varying quantities, according to the general condition of these patients, and yet I do not suppose that indican is the active poison. It would be as foolish to affirm this as it would be to judge of the results of heat and power produced in a steam furnace by analyzing the character of the slag in the ash pan. Very much more exhaustive studies in the chemistry of digestion are necessary before we begin to approach any true knowledge of the active agents producing these effects.

But it is not necessary for us always to wait in medicine for scientific facts before attempting treatment. Some of the most valuable remedies that we have at our disposal are purely empirical in their origin. When a patient presents these evidences of toxemia he can be materially helped by a certain regimen and treatment, no one particular element of which is necessarily curative, but all of which combine to give relief.

First, Diet: This cannot be laid down in a uniform manner for all patients. The majority of them, I believe, do not digest milk well, and eggs as a rule do not agree with them, though occasionally raw eggs will be digested when cooked eggs will not. Meat of all kinds seems to me to agree very well with this type of patient, but meat soups are not well digested, and therefore cream soups are preferable. Fish in all forms and oysters usually agree with such patients, and also certain types of vegetables; but potatoes, turnips, beets, and tomatoes are liable to give more trouble than other vegetables. Rice, macaroni, and hominy are usually well borne, but should not be cooked with cheese, and cheese as a rule is not well digested. Patients differ entirely from each other in their capability to assimilate breads and sweets, and it will not do to lay down any rule for the use of these articles; in fact, in these cases various forms of diet and various articles of diet should be tried until the articles which disagree are ascertained.

Fluids: Tea almost uniformly disagrees with these patients, making them nervous and increasing their indigestion. In many of the patients coffee acts as a desirable and pleasant stimulant, both in the morning for breakfast and after dinner, and does not in any way interfere with sleep. In others it acts as a poison and should be excluded. I believe that in all these cases alcohol should be avoided in every form, especially the sour wines and champagne. In about one-

half of the cases whiskey can be taken without ill effects, but the stronger wines, like port and sherry, and all liquors are to be avoided. Occasionally a patient can take Rhine wine diluted, or the Austrian Vöslauer, without ill effects. Water should be taken very freely, and a good alkaline or lithia water is often of much benefit.

Drugs: The digestion must be aided in these patients by two classes of remedies: one which stimulates the liver to activity, the other which counteracts the evolution of toxic agents in the intestines. First, it is my habit to give these patients small doses of calomel (gr. $\frac{1}{10}$ every half-hour till one grain is taken) every ten days and to give them a dose of podophyllin (gr. $\frac{1}{4}$) every ten days alternately with the calomel. It is also well to stimulate the liver by the use daily in the morning of either Carlsbad salt or a salt made by mixing gr. x of salicylate of sodium with ʒj of phosphate of sodium and ʒss of chloride of sodium. If this mixed salt is put in a large tumbler of sparkling water of any kind, and taken during the act of dressing in the morning, it will usually be beneficial. In this manner the liver is stimulated to action.

The second object—the counteracting of the toxic agent—is attained by one of three different remedies, and it is never possible to determine exactly which of these three in any one case will prove of service. The first is a combination of gr. v of the sulphocarbolate of sodium with gr. j of permanganate of potassium put up in a capsule which is coated with shellac so as to be insoluble in the stomach, and hence dissolve only in the intestine. Such capsules are given after each meal and on retiring. The second remedy that I use is a capsule of salol and castor oil—gr. v of salol and ♏x of castor oil. This also is rendered insoluble in the stomach by a coating of shellac. The third remedy is given in the same manner, in capsule after eating, and consists of benzoate of sodium, gr. ij; sulphocarbolate of zinc, gr. j; and betanaphtol, gr. j. It is my experience that by the administration of these remedies continuously for a considerable period a steady amelioration in the symptoms of intestinal indigestion will ensue, and, what is much more noticeable, an entire cessation in the periodicity of the alternations of the symptoms; the first evidence of relief being a quieter rest during the night, without any early awakening and a relief from the depression that occurs early in the morning.

Baths: The use of a hot bath on rising, at a temperature of 104° F., for three minutes, followed by cool sponging for one-quarter of a minute, is of importance, as nothing stimulates the general nutrition of the body better than such a measure; but in this type of patient the cold bath in the morning usually produces distress, and is followed by a feeling of exhaustion, cold extremities, and discomfort.

Exercise and Rest: In all cases an increased amount of exercise should be insisted upon, yet in many cases any long-continued exercise is most exhausting and is followed by a rapid action of the heart; hence, it is far better for these patients to swing clubs briskly or to play a game of tennis for twenty minutes, thus getting into a pleasant perspiration, than it is to take an hour's horseback exercise or to play a game of golf which requires tramping two miles, though both of these measures occasionally can be endured and are beneficial. One very important element in the treatment is regularity in the amount of rest. These patients should be urged to lie down and relax all the muscles, the clothing being properly loosened, for one-half hour after each meal, and after any active exercise rest of the same duration should be enforced. One of the essential elements of successful treatment in these patients is a pleasant occupation for the mind, as their depression leads them to intensify their nervousness by introspection and self-observation. A variety of occupation should be sought, and every means should be employed to keep them interested and diverted. An outdoor life is far better for them than a life indoors, and therefore if an occupation can be found which involves some activity in the open air it is desirable: the study of botany, the study of forestry, the running of a farm, the care of chickens, the occupation of an engineer or surveyor, the study of landscape gardening—all of these are pleasing occupations for men and women, and it is on this principle that travel and change of scene may be urged upon these patients. But whatever means are employed in their treatment, it seems to me that the essential element in their success is the counteracting of the toxic product within the body and the prevention of its formation.

ON THE EVILS ARISING FROM THE FAILURE TO RECOGNIZE THE TRUE NATURE OF NEURASTHENIA, AND SOME CAUSES OF THIS FAILURE.

By W. W. JOHNSTON, M.D.,
OF WASHINGTON, D. C.

One of several ways might be selected to demonstrate the truth of the proposition that there is a very general failure to make a correct diagnosis in cases of neurasthenia, and that prolonged and unnecessary suffering arises from this cause. A report might be made of a number of cases in which such failure had resulted in prolongation of illness through years. This series of cases would have a remarkable uniformity in showing how the disorder of the nervous system had entailed a degree and amount of suffering that could not be adequately described. It would also show how thwarted and exhausted energies had hindered the normal development of the individual, or had, as is often the case, wrecked his life.

The unusual uniformity in the history of such cases and the sameness in their symptoms and progress would give to such repetition more monotony and tediousness than I care to be guilty of. Beside, I am sure that my general statements of fact will be concurred in by all present who have to do with the phenomena of this disease.

Another way to present this subject is to report a typical case embodying the main features of the class and to let the facts show the truth of the proposition. With this object in view, the case of Charles Darwin has been chosen, as it includes every essential fact necessary to show the evil arising from the failure to carry out a

proper treatment of neurasthenia, and has, moreover, a certain amount of subsidiary interest that makes it a more striking example.[1]

There is no contemporaneous opinion as to the nature of Darwin's illness and no published opinion since his death that give any adequate explanation of his prolonged sufferings. The facts in Darwin's case, stated briefly, are these: He was in perfect health up to his twenty-second year, with a strong frame, possessed of great endurance and fondness for outdoor life and field sports. At twenty-two years of age he sailed on a five-years' cruise as naturalist of the "Beagle." The discomforts of ship life in a narrow cabin, the exacting nature of his work in observing phenomena, in collecting specimens, and in taking notes in the departments of botany, zoölogy, geology, and ethnology combined to tax his energies to the utmost. In addition to the mental overstrain involved in such work, his life on shore was one of great physical fatigue. He was never at rest on reaching port, but took every opportunity to visit distant points of interest, to climb mountains, and to study the fauna and flora over extended areas of country. Many journeys on horseback were undertaken through sparsely settled districts, where food and sometimes water were difficult to obtain and where every discomfort and hardship from cold, wet, and exposure had to be endured. He was often ten hours in the saddle without food or rest, and frequently at his journey's end was exhausted from hunger and fatigue. Journeys on horseback of 100, 200, and 400 miles were accomplished, and one of 300 miles in an open boat, off Terra del Fuego, was especially notable for its hardships.

The voyage ended in 1837, when Darwin was twenty-seven years of age. That the overstrain of the "Beagle" voyage was the probable cause of the beginning of his ill-health is shown by the fact that symptoms of illness are spoken of soon after he landed. He writes of being unwell during the two years and three months between his arrival and marriage. The three years between his marriage and the date of his abandoning London for the country were marked by frequently recurring illnesses and one long and serious illness, the

[1] A paper dealing more fully with the nature and causes of Darwin's ill health was read by me before the Anthropological Society of Washington, and appears in the "American Anthropologist," January-March, 1901. What is here stated as to Darwin's life and illness is an epitome of the facts presented in that paper.

nature of which is not fully described; it is to be inferred, however, that they were all of the same kind as those that followed. His increasing weakness, the inability to meet scientific friends or attend society meetings, and at the same time to carry on his projected scientific work, forced him to take the resolution to leave London for the country.

At Down, his new home, he grew rapidly worse, and from the pages of the *Autobiography* and the *Reminiscences*, written by his son, as well as from his published letters, a clear idea can be formed as to the nature and extent of his sufferings. The symptoms here described are these: Violent shivering, giddiness, and vomiting after prolonged conversation with friends, great sensitiveness to heat and cold, insomnia, a tendency to muscular fatigue after slight exertion, emotional disturbances, headache, mental depression that was sometimes profound, palpitation and distress in the region of the heart, and continued disorders of digestion. These symptoms bore a close relation to the amount and character of his work and to the strain of social life. "Anything," he wrote, "that flurries me knocks me up afterward and brings on a violent palpitation of the heart." Half an hour, more or less, of conversation would make to him the difference of a sleepless night and of the loss, perhaps, of half a day's work. Any departure from the regular routine of his life upset him for hours, and the anticipation of leaving home caused a "miserable sinking feeling," although the cessation of work and absence from home always did him good.

Darwin's life at Down began in 1841. The symptoms of illness increased as the years went on. After ten years he rarely went to London, and he gradually abandoned all social life, going nowhere and receiving but few friends at home. In 1857 he wrote that his health had quite failed, and his work is spoken of as a burden from which he would gladly be freed. He was often confined to the house for weeks at a time, and suspects at this time that he will soon entirely fail, and believes that he must husband the little strength left in order to finish his work. For weeks, sometimes for months, he could do little or no writing, although it was only when confined to his bed that he gave up all occupation.

It is the same story of ill-health, of suffering, of despondency and exhaustion from 1839 to 1872, a period of thirty-three years. From

the year 1872 an improvement set in that gave great "satisfaction and hope to his family," and during the ten years from 1872 to 1882 there was an alleviation in many of the most distressing symptoms. He had during this time less general discomfort, less insomnia and despondency, and was able to work more steadily. Toward the latter end of this period, although the symptoms connected with the nervous system were much relieved, there was a gradual loss of physical vigor with frequent complaint of pain or uneasiness about the heart. In 1881 occurred the first of many attacks of angina pectoris, and from this time there is a history of arteriosclerosis with progressive heart-weakness, ending in death on April 19, 1882. His age was seventy-four.

The amount of work accomplished by Darwin from the date of his return home in 1837 until his death in 1882 is incredible when the state of his health and the constant suffering under which he labored are considered. Given an established state of neurasthenia in 1837, it is easily seen how this was aggravated by the nature and character of the work done, and in this we will find a sufficiency of causes to produce the symptoms enumerated.

During this time he wrote twenty-three distinct and important works. This does not include new editions and reviews nor the books that he edited and superintended through the press. He also published fifty-one papers and communications to scientific journals. Mere numbers, however, give no adequate idea of the amount of labor done in investigation and in an extensive correspondence, nor of the strain of the intense and sustained application of the mind and the use of faculties of the highest order to the accomplishment of his tasks.

Much more might be said to show the relation between the origin and continuation of the neurasthenic symptoms in Darwin's case and the causes that induced them, but the point to which I wish to draw attention is that the failure to apply an early and radical treatment led to great suffering during a long period. That Darwin did not break down entirely was due to the modified rest treatment under which he lived during many years. Whether this was begun and continued under Sir Andrew Clarke's advice there is no way of knowing; but it undoubtedly saved Darwin from complete collapse and made it possible for him to live and work.

His day's programme was as follows, and it will be observed how well suited it was for the existing conditions: 7.45, breakfast; 8 to 9.30, work in his study; 9.30 to 10.30, rest in the recumbent position, with reading aloud; 10.30 to 12, work in his study; 12 to 12.30, short walk out-of-doors; 12.30, luncheon; 1.30 to 2, rest in the recumbent position; 2 to 3, writing of letters; 3 to 4, rest, lying down in bed-room, with reading aloud and sleep; 4 to 4.30, a short walk out-of-doors; 4.30 to 5.30, work in his study; 6 to 7, rest in bed-room and reading aloud; 7, simple supper; 8 to 10, in drawing-room, games, reading, etc.; 10.30, in bed.

These rules, it will be seen, allow five hours of what may be called work, including letter-writing, this time being divided into four periods of one hour to one and a half hours in length; there were three and a half to four hours of rest during the day, lying down, the time being divided into four periods of about one hour each. There were two short outings, one of one hour or one and a half hours in the morning and one of about the same length of time in the afternoon. Eight hours and a half were spent in bed at night.

The problem with Darwin was how a man suffering with such symptoms could best continue an arduous life of intense mental application during the many years necessary to complete a great task. Darwin certainly solved the problem; the task was completed in spite of suffering and exhaustion.

There can be very little question, however, in view of the benefit derived from the lessening of the hours of work and from the effect of diversions and holidays, that if Darwin, on his return from the "Beagle" voyage, had abandoned work altogether and had devoted one or two years to an effort to regain lost strength he probably would have been cured, certainly benefited, and that his afterlife would have been more full of joy and alleviation than it was.

Darwin's case does not differ in any material way from a large number met with in everyday experience; it serves the purpose of this paper in showing what serious evils follow the neglect to insist upon the entire abandonment of all work in the earlier stages of neurasthenia. My experience is, I am sure, not peculiar in meeting with patients who, not having been advised with sufficient urgency to follow this course, repeat the story of work continued during many years under every possible hinderance and discourage-

ment. The results obtained under such circumstances are, as a rule, imperfect, and success purchased at so great cost of ill-health brings with it no adequate compensation.

Worse than this, it is not rare to see careers entirely ruined by the early establishment of a neurasthenic state, with the loss of all self-confidence and energy, and there is but a narrow margin, which is frequently crossed, between the mental depression of neurasthenia and suicidal melancholia.

No matter how serious are the symptoms presented in a case of neurasthenia, cure is the usual result if the treatment is radical enough and continued for a sufficient length of time. That some cases are not curable by any mode of treatment must be admitted. Incurability, however, does not belong to the early stages of the disease, but to the latter periods of cases that have lasted for years without proper treatment, although they may have wandered the world over in the vain search of health.

The reasons for the failure to apply early treatment are too numerous to rehearse. The unwillingness of patients to recognize the true nature of their symptoms and to submit themselves unreservedly to the advice of the physician are very obvious causes in many instances. Within recent years new obstacles to prompt and thorough treatment have arisen in the development of specialism. A malady that shows functional disturbance in every organ in the body is an attractive field for special therapeutists, as it shows a ready point of attack from whatever side it is seen. It is difficult indeed to avoid a bias where the cries for help come from the eyes, stomach, intestines and genital organs, the heart, every nervous center and every nerve, and where every special method in turn so fully satisfies the patient's demand.

Goodell's paper on the "Abuse of Uterine Treatment Through Mistaken Diagnosis" (*Medical News*, December 7, 1889) served a good purpose. It is time for some representative of each specialty to point out the hinderances to cure that are found in the honest attempts in his department to empty the ocean by draining the water of the bay. What Goodell calls the "positive exuberance of symptoms" in neurasthenia makes the diagnosis difficult unless the simple combination is known that unlocks the door and shows the whole interior at a glance.

At the present moment a frequent mistake is in attributing general nervous symptoms to gastric disorder and resorting to diet or local treatment. The effect of this is to satisfy the patient's reason and benefit him to a limited extent, but it leaves untouched the essential cause of the disease and indefinitely postpones its cure. As a rule, indigestion of this nature is quickly cured by rest and feeding, and the futile attempts to get relief by lavage, diet, and drugs alone postpone the adoption of radical and necessary procedures.

Another hinderance to the prompt and thorough treatment of neurasthenia is the general want of the appreciation of its symptoms among young medical graduates. The improvement in medical education would lead us to expect more precise knowledge on the subject. The tendency is to totally ignore or minimize characteristic symptoms, or to explain them as depending on conditions that are themselves the result of the disorder of the nervous system. There is no gainsaying the assertion that, as a consequence, there is among the rank and file of the profession a general misapplication of treatment to the conditions found. What are the reasons for this it would be difficult to say; but if physicians are to meet the problems of ill-health among the overtaxed business and professional men of this busy country they will have to receive more exact instruction in the diagnosis and treatment of neurasthenia than is now given them. If this were done we would have less uncertainty, more decision and promptitude in dealing with this disease, and would turn many such sufferers from the doors of the charlatans of all sorts which they now crowd in the vain expectation of relief. There would be less disposition to resort to therapeutic measures designed to impress the imagination of these patients, and the effort would be made to treat them with reason based upon a knowledge of the true pathology of the disease.

The difficulties met with in treating all but the mildest forms of neurasthenia in their own homes, and the rapid improvement when all the surrounding conditions are favorable, create the demand for special institutions for this purpose. Hospitals for mixed cases do not answer for these patients. They need sanatoria properly constructed and equipped with every device to secure rest, quiet, and seclusion.

Forms of mental disturbance should not be treated under the

same roof with neurasthenic patients; these are always sensitive to sights and sounds, and are injured by association with the insane as well as with inebriates and opium habitués.

There is in this country a great opportunity for the development of the institutional treatment of neurasthenia; but such institutions, to be successful, must be constructed and managed for neurasthenic cases only, and under the care of men specially trained for this work; the management and methods must be such as to guarantee honesty and ability, with complete freedom from every suspicion of charlatanry.

DISCUSSION.

DR. CABOT: In the treatment of the type of neurasthenia supposed by him to be toxic, I understood Dr. Starr to say that calomel and podophyllin were useful as hepatic stimulants. It is now three years, I think, since Dr. Franz Pfaff showed this to be a mistake, and it seems to me it is time now to give up the use of those terms.

DR. PUTNAM: There is abundant opportunity for differences in opinion regarding the origin of neurasthenia, since the conditions are so complex. It does not seem to me that Dr. Starr has proved his case in regard to its toxic cause. We have had neurasthenia attributed to uric acid and to a variety of similar conditions, but the connection has never been proven. It is not my experience that the form under consideration occurs only in cases where digestion is disturbed. As regards "the varying intensity of the cause corresponding to the varying intensity of symptoms," it seems to me that is not the correct principle to work upon. Many neurosal states dependent on a fixed cause show these periodic exacerbations of an earlier generation. I was many years ago struck by the statement of Verneuil, a French surgeon, that the neuralgia associated with healing of wounds is periodical, and I see no reason why we should consider that these cases belong to a different class.

Again, because a disease is cured by a certain remedy, we cannot argue with any degree of probability that we have found the cause. The vicious circle of disease may be broken up by many influences that have nothing to do with the formation of that circle originally. I was going to say what Dr. Cabot did about the various eliminants, especially those that act on the liver, I also believe that it is more than doubtful whether we can influence the action of the liver in that way. Other means of treatment, too, such as Dr. Johnston has alluded to, for example, are just as effective in this class of cases as in others. I would like to express my indorsement of what Dr. Johnston said concerning the establishment of sanatoria. They are badly needed in this country.

DR. HERTER: I should like to say a word in regard to the relation between mental depression and the occurrence of intestinal putrefaction. I am sorry Dr. Starr did not state in his paper what he considers that relationship to be. A number of years ago, when studying melancholia, I found the ethereal sulphates regularly and largely increased in this condition. I have observed since, in many cases falling short of melancholia, a regular relationship between the ethereal sulphates and indican and the mental depression; the indican diminishes and the ethereal sulphates diminish as the patients come to feel better, whereas, if the patient becomes more depressed these substances occur in increased amount. Whether the relationship is one of cause and effect is, of course, another question; but in some experiments a few years ago, on the administration of indol to the human subject, I found that under certain conditions the doses were followed by very marked nervous symptoms, by increased irritability of the nervous system, and subsequently by depression of function, which made it necessary to give up the experiments.

The criticism made by Dr. Cabot on the action of calomel as a cholagogue appear entirely justifiable. The action of calomel in these cases can be explained in a simpler way, and by supposing it to act as a cholagogue. The use of calomel is followed by rather free movements, and during the period of diminished absorption the excretion of ethereal sulphates is small and the patients feel temporarily relieved.

DR. BAUMGARTEN: I would like to call attention to one of the reasons why it is difficult for us in individual cases to trace the causes of neurasthenia that arise from mental overwork to their true source. We have not so good an apparatus for estimating mental fatigue as for judging muscular fatigue. The man who does a hard day's muscular work feels fatigued immediately, but the mental worker does not perceive his fatigued condition or is stimulated by it to even greater effort, and habitually overworks until he reaches the dangerous period, when he breaks down.

DR. STARR: I will call attention to the fact that I presented these cases as being one of several classes of neurasthenia, and have not said that all cases of neurasthenia conform to that type. In the beginning of the paper I classified neurasthenics in four groups, of which the toxic group came last. My study of neurasthenia has been a pretty wide one, and in trying to differentiate different types it has seemed to me that there is a class distinctly toxic in origin in which this periodicity of symptoms occurs, and which responds to certain remedies. I am more and more failing to diagnosticate primary neurasthenia, and am more frequently finding neurasthenia secondary to other diseases.

I am perfectly familiar with the recent literature from Dr. Pfaff's laboratory on the subject of the action of calomel and podophyllin and their effects upon the liver, and, of course, I know perfectly well that calomel and podophyllin do not actually stimulate the liver; but they do, by their purgative

action, wash out of the intestines a large amount of bile, and they produce certain chemical changes in the intestines that lead to renewed activity on the part of the liver. You may call that what you please, but the practical effect produced is what we want in the way of stimulation of the liver; it may not be at all by increasing its secretion of bile, but rather by producing other effects which aid metabolism.

TWO CASES OF STREPTOTHRICAL INFECTION: DEMONSTRATION OF A STREPTOTHRIX, OR BRANCHED TUBERCLE BACILLUS, IN THE SPUTUM.

By JOHN H. MUSSER, M.D, and NORMAN GWYN, M.D.

ABSCESS OF THE BRAIN DUE TO A STREPTOTHRIX.[1]

By JOHN H. MUSSER, M.D., R. M. PEARCE, M.D.,

AND

NORMAN GWYN, M.D.,

OF PHILADELPHIA.

Case I.—J. T., aged thirty-seven years, male, married; very active in business; under the care of Dr. Dercum for mental disorder of several months' duration. I was asked to see him September 25th because of slightly increased respiration, pulse-rate, and temperature without apparent cause. Physical signs of bronchitis of very moderate amount were found. A slight morning cough was observed. The temperature until October 30th was about 99⅘° to 100⅕° in the evening; the pulse was 100 to 125. The mental symptoms, confusion, and some excitement continued. He gradually became more dusky and the respirations more frequent. He had sweats during this time, and lost weight. The physical signs of bronchitis became more marked and the heart became dilated. On the evening of October 30th the temperature began to rise, reaching 104° November 3d. Physical signs of bronchopneumonia developed, and death took place November 6th from exhaustion, due to dilated heart, which also caused œdema of the lungs. The blood, the urine, and the sputum were examined as frequently as the state of the case permitted. Of the first two nothing could be obtained to throw light on the case. The *urine* was always of normal specific gravity; contained a trace of albumin, no sugar, and few hyaline casts. The *blood* did not show leukocytosis. The one count reported is typical of all. The hemoglobin was 80 per cent.; red blood-corpuscles, 4,572,000; white blood-corpuscles, 3200.

[1] See "Streptothrical Infection," by John H. Musser, M.D. Phila. Med. Journ., and Trans. Chicago Medical Society.

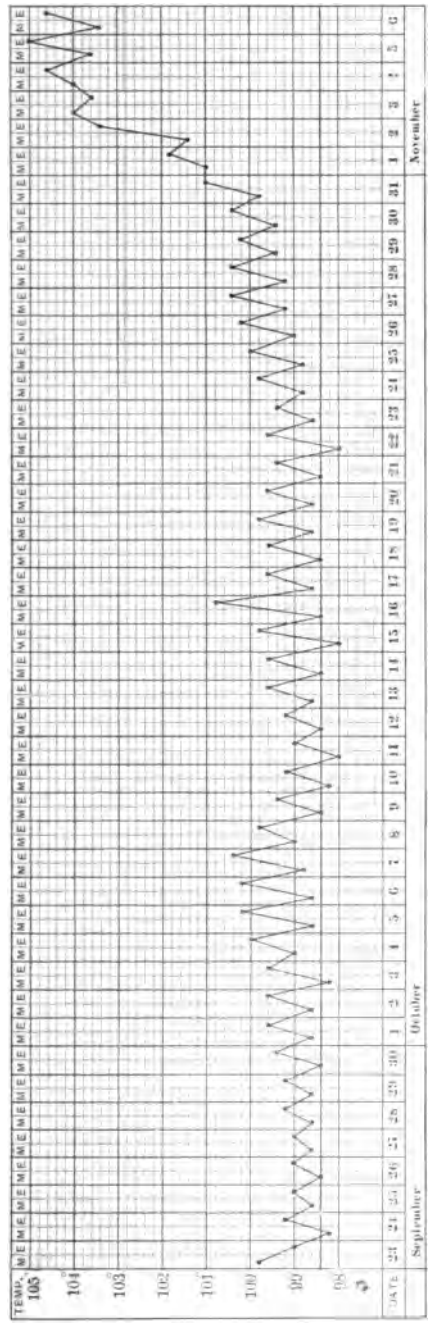


Chart of Case I.

Of the whites there were: polymorphonuclear, 79 per cent.; small mononuclears, 17 per cent.; large, 3 per cent.; transitional, 1 per cent.

The sputum was studied most carefully by my associate, Dr. Norman Gwyn, and to him I am indebted for the suggestion of the nature of the infection. His report is as follows:

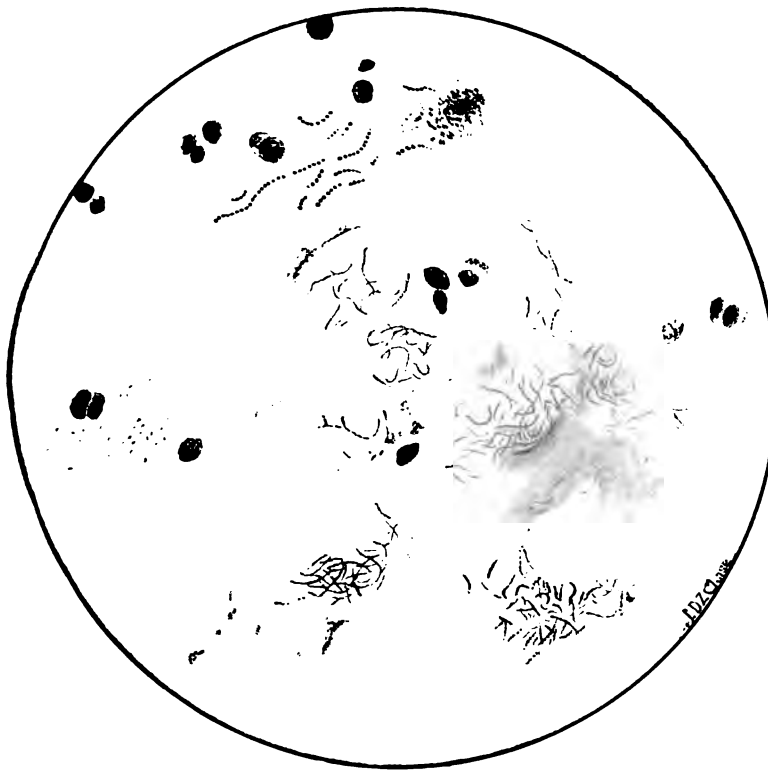
The *sputum* first obtained was small in amount, yellowish, homogeneous looking; not foul, and contained no blood. No granular masses were present. Unfortunately, after the second day the stuporous condition of the patient seemed to prevent the collecting of pulmonary discharges, the later specimens being only nasal mucus and buccal secretion. The first examination showed apparently a few thin tubercle bacilli retaining faintly the red stain of carbol-fuchsin after counter-staining with Gabbett's methylene-blue. Owing to the filiform appearance of one of these, further examination was made and revealed, in addition to small rod-like forms, some definite branching structures resembling those pictured by several of the before-mentioned authors. No rosettes or club-like bodies were present. Many presented bevelled ends and were present as short filaments. By Gram's stain principally rod-like forms, containing the round coccus-like bodies (polychromatosis), were to be found. Some showed true branching. The organisms were extremely few. The rod-like forms, *by themselves*, could readily be mistaken for tubercle bacilli. Only in the specimens stained by Ziehl-Neilsen and Gram's method were definite streptothrical filaments found. Great numbers of streptococci and pneumococci (?) were present, which caused the death of the guinea-pig in ten days without any signs of streptothrical or tubercular lesions. As I have mentioned, after the first two days no true sputum was obtained. After the second day the nasal and oral secretion showed no organism like those found in the specimens of the first days. Cultural experiments had no results. The definitely branching structures and the appearances presented by Gram's and Ziehl-Nielsen stain, together with the resemblance to previously described streptothricæ, induced us to suppose that we had to do either with a primary streptothrical infection or one secondary to a streptococcus infection of the bronchial tract. The possibility of these organisms being branched forms of the tubercle bacillus must also be considered.

Plate I. shows the filamentous and beaded rod-like forms found with Ziehl-Neilsen stain. From the grouping and the fact that the organisms are nowhere scattered through the field, but gathered in clumps or masses, one gets the idea that they may represent small mycelial tufts.

Plate II. shows the rod-like forms with their coccus-like spores. Only very occasional branching is here to be seen.

Case II. is of extreme interest, and is the first of its kind to be reported in this country. It is, however, a very accurate picture of that described by Sabrazes, Riviere, and is very similar to those of Eppinger, Ferri and Faguet, Aoyama and Chiari. Clinically, it is of

PLATE I.



Sputum, Case No. 1. Carbol-fuchsin and methylene blue (Gabbet's). Filamentous and branching forms.

PLATE II.

Sputum, Case No. 1. Gram stain. Rod-like forms, with round coccus-like contents.

importance as showing how large an area of the brain can be affected without giving rise to localizing symptoms, and how difficult the diagnosis of such condition may be. Further, it may explain the nature of some of those instances of cerebral infection, particularly abscess, in which neither by culture nor by animal inoculation can an infective agent be discovered.

The history of this case was as follows:

CASE II.—C. H., single, aged twenty-four years. Complaining of an attack of loss of consciousness, with later nausea and vomiting. His father had died of pulmonary tuberculosis. He had always been fairly well; habits good; had gonorrhea some years ago; no lues; no history of lung trouble; no ear disease. Had some small operation on nose recently.

Was quite well up to Wednesday, February 6th, when he had severe headache. The following day while at work he felt uncomfortable, and in a few moments lost consciousness, falling to the floor and biting his tongue. He was quite alone, so that nothing further than this could be ascertained. The patient felt dazed and stupid and noticed numbness of right arm and leg, with some twitching of these members. On Friday he felt better; on Saturday and Sunday he was much the same. On Monday, the 10th, another attack, distinctly convulsive and resembling epilepsy, occurred. The numbness of right arm and leg was a little more pronounced, and the occasional twitching was evident. There was slight headache, no chills, no cough, no pain or discharge from the ears, no eye symptoms.

Seen by Dr. Dercum at this time no definite localizing symptoms could be made out. Present condition persisted. There was no fever. The patient remained fairly well and was conscious. Pupils were equal; tongue heavily furred. The pulse was fair and the patient seemed to be improving. There was, however, slight hypæsthesia of the right side.

On Wednesday morning about 9 o'clock, after a fair night, there was, according to the nurse, a sudden collapse. The pulse could not be felt at the wrist. When seen half an hour later the pulse was very slow (30 to 50), very irregular, but of fair volume. The patient was semi-conscious, answering only when shouted at. The patellar reflexes seemed exaggerated, especially on the right side. There was marked hyperextension of both feet. The Babinski reflex was marked on the right leg; Kernig's sign well marked; very decided ankle clonus. Heart, lungs, and abdomen negative. Feces and urine were being passed involuntarily; some cyanosis of the nose and ears beginning. There was no rigidity of the neck, nor any tenderness over the skull. The examination of the eyes by Dr. de Schweinitz showed deviation of the left eye; pupils negative; very marked edema of the disks, probably due to meningitis. The patient was unconscious by evening; pulse was irregular and variable; distinct Cheyne-Stokes respiration. Prof. Hare joined in the consultation.

Lumbar puncture was performed. Two ounces of turbid fluid contained a few leukocytes, but no bacteria were obtained. There was immediate improvement, the patient regaining consciousness and remaining so until 6.30 next morning, Thursday. Lumbar puncture was repeated, with no improvement. The patient lapsed again into a semi-conscious state; rigidity of the right side became quite marked. Occasional convulsive movements were, however, sometimes seen on the left, and a general convulsion, apparently of pontine origin, occurred. The hyperextension of the feet was extreme, the dorsæ of the feet being level with the tibiæ. No rigidity of the neck; reflexes still exaggerated; Babinski's reflex still present. The patient gradually failed, dying at 6.30 P.M. on Thursday, one week from the onset of the first convulsion.

The temperature, though subnormal at first, began to rise in the last three days, and for twenty-four hours before death was between 103° and 105°. The pulse increased in frequency meanwhile, but lost very much in volume. Apart from the slight deviation of the left eye, slight impairment of sensation on right side, no paralyses or localizing symptoms were observed.

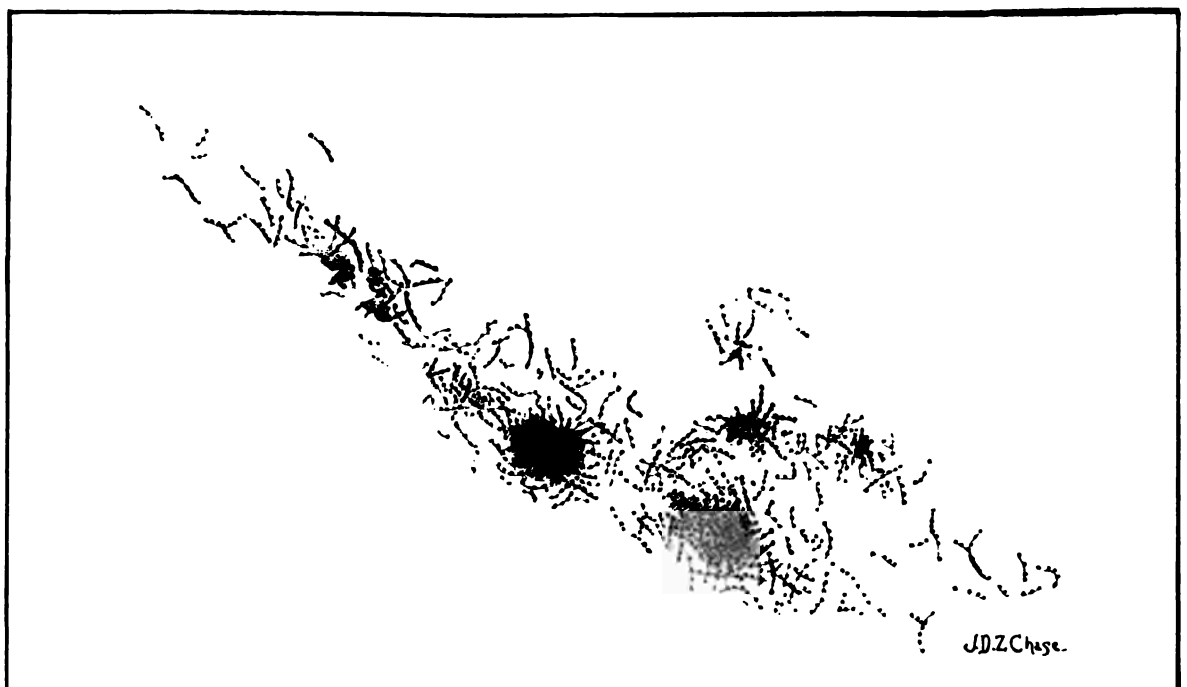
The autopsy and the histologic, cultural, and experimental examinations were made by Dr. R. M. Pearce, to whom we are indebted for much care in prosecuting the inquiries.

Head only Examined. Scalp and calvarium not noteworthy. Dura mater normal; pia normal; posterior and upper portion of upper hemisphere prominent. At a point just posterior to upper portion of fissure of Rolando is an area 3 cm. in diameter, which is fluctuant, grayish-yellow in color. On section there is found at this point, principally in the white matter of the hemisphere, but also involving the cortex, a cavity 3½ cm. in diameter, containing a thick fluid, the first portion of which to escape is chocolate colored, the remaining portion is grayish-yellow and of the consistency of oil. No granules resembling those of actinomyces were present. The cavity is lined by a thin greenish-gray necrotic membrane, beneath which the brain tissue is much injected. The odor of this pus is exceedingly foul. Brain tissue surrounding abscess for the distance of 2 to 3 cm. is softened and yellow in color, though there is apparently no direct extension of the inflammation.

Macroscopically there is no inflammation of the pia over abscess. The rest of the brain on section is normal. There is no evidence in the vessels of the brain of arterial disease, thrombosis, or embolism. Bony ears are normal, and nowhere in the skull is there evidence of necrosis or bone-disease.

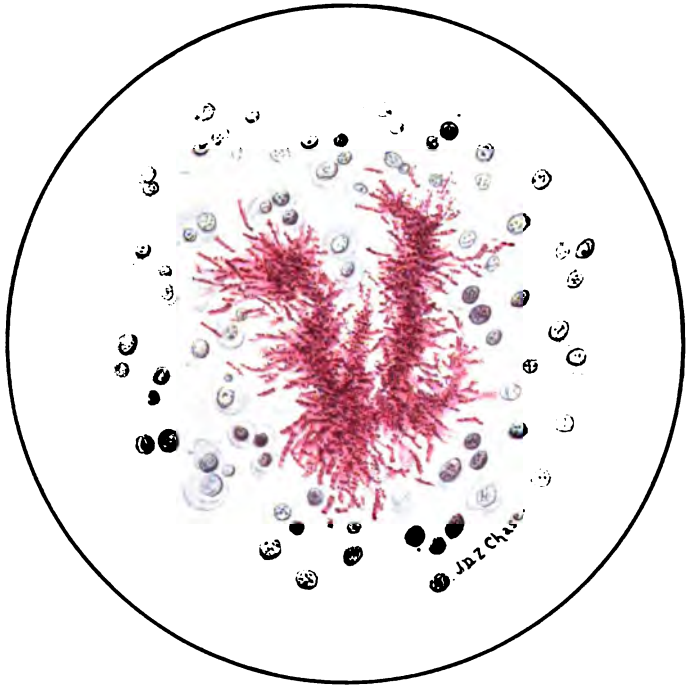
Smears from the abscess contents showed no tubercle bacilli, and only after prolonged search and staining by carbol-fuchsin, followed by Gram's solution and decolorization by anilin oil, could anything be made out. In one of these specimens was found a large ball-like and tangled mass, made up of long, thin filaments, staining irregularly. (Plate III.) There is some suggestion of branching at the periphery of this mass. Only the one clump of these organisms was found. Cultures, aërobic and anaërobic, were quite negative.

PLATE III.



Streptothrix mass as seen in smear preparations from contents of brain abscess. Stained by modified Gram-Weigert method, 1/12 in. homog. immersion objective.

PLATE IV.



Section through wall of brain abscess showing character of streptothrix colony. Stained with hæmatoxylin, followed by modified Gram-Weigert method, 1/12 in. homog. immersion objective.

Inoculations of two guinea-pigs were made, subcutaneous and intraperitoneal. The first of these died in nine days, nothing suggestive being found; the other being killed after thirty-two days, and showing nothing but a few miliary nodules at point of inoculation in the peritoneum. No evidence of tuberculosis in either animal. Cultures from both were negative. Histologic examination negative.

A histologic examination of the wall of the abscess of the brain showed the inner edge to be composed of necrotic pus cells, indicating its chronicity, the deeper layer of fairly well-preserved pus cells, lymphoid cells, and occasional endothelial cells. In the adjoining brain tissue lymphoid and plasma cells were quite numerous. About the bloodvessels at periphery of abscess are many lymphoid and pus cells. The surrounding brain tissue shows degeneration with infiltration by polymorphonuclear leukocytes. No evidence of tubercles or tubercle bacilli.

Sections stained with carbol-fuchsin, potassium iodid and iodin, and decolorized by anilin oil, show in one spot a large mass of threads radiating from a common center. (See Plate IV.) At the periphery, where the arrangement of individual elements are loose, they appear as long, thin threads, with small, irregular staining. The general appearance is that of the center of a colony of actinomyces. No clubs or rosettes are, however, present. Along the edge of abscess wall a few single threads, similar to those in the original smears, were found.

Twenty-six cases are reported by eighteen observers. The sexes were indiscriminately affected, but all were in adult life. Four of them presented cutaneous and subcutaneous lesions, but one alone of these four had no lesions elsewhere (Case I.). In six cases death was due to intracranial abscess, in two of which no other lesions were reported. One of the remaining four had the bronchial glands affected, one had bronchopneumonia and two bronchiectasis, all possibly primary, due to the infection which caused the intracranial lesion. Two of the twenty-six died of meningitis, in one of which class an endocarditis was found, with the streptothrix as causal of both lesions.

The pulmonary lesions were predominant. Excluding the lesions of the bronchial glands above referred to, in eighteen the lungs or lungs and pleura were infected. One was said to have pulmonary symptoms, one had tuberculosis and pleurisy, one had influenza-like symptoms. Eight of the patients had bronchopneumonia, one having also empyema, and two terminated in gangrene and in abscess of the lung respectively. One of the eight patients with bronchopneumonia had cerebral abscess, presumably metastatic, perhaps from

the bronchial glands. One of the eight had bronchiectasis. Two of the eight bronchopneumonias had cutaneous infections, and had no complications.

Three of the eighteen pulmonary cases had abscess of the lung, one having bronchopneumonia—as mentioned above—and one empyema. Four were victims of bronchiectasis, one of which had bronchopneumonia and one gangrene of the lung. In addition to the one case of gangrene of the lung with bronchiectasis, three cases of pulmonary gangrene were reported by A. Ucke.

To these must be added one case of noma and one of subphrenic abscess.

It is thus seen that nineteen at least of the cases had some pulmonary infection. Of the remaining, one (cerebral abscess) at least did not come to autopsy (chest not examined).

It does not seem unwarranted to judge that the infection atrium and primary lesion are in the respiratory tract.

Reporter.	Clinical course.	Microscopic examination.	Cultures.	Inoculation.
1. Rosenbach,	Erysipeloid.	Branching thread-like organisms.	Positive.	Positive.
2. Naunyn,	Endocarditis meningitis.	Branching threads.	Negative.	
3. Almquist,	Cerebrospinal meningitis.	.....	Positive.	
4. Eppinger,	Abscess of brain, infection of bronchial glands.	Branching threads.	Positive.	Positive.
5. Bucholtz,	Bronchopneumonia; empyema.	Branching threads; streptothrix.	Negative.	Negative.
6. Sabrazes and Riviere,	1. Abscess of brain; small abscess kidney; bronchopneumonia.	1. Organisms found.	Positive.	Positive.
	2. Bronchopneumonia.	2. Organisms found.	Positive.	Positive.
7. Ferri and Faguet,	Abscess of brain.	Characteristic organisms.	Positive.	Negative.
8. Flexner,	Bronchopneumonia; pseudotuberculosis.	Characteristic organisms.	Negative.	Negative.
9. Schule and Petruschky,	Influenzal-like illness; pleuropneumonia; pustular exanthem.	Characteristic organisms in sputum and skin pustules.	Negative.	Negative.
10. Fullerton,	Pulmonary and cutaneous inflammations.	Characteristic organisms in sputum and skin.	Negative.	Negative.
11. Rullman and Ziemssen,	Abscess of lung; bronchopneumonia.	Characteristic organisms.	Positive.	Positive.
12. Aoyama and Myamoto,	1. Pulmonary abscess;	1. Characteristic organisms.	Positive.	Positive.
	2. Tuberculosis; pleurisy	2. Characteristic organisms.	Positive.	Positive.
13. Larkin & Norris,	1. Gangrene of lung, bronchiectasis.	1. Characteristic organisms.	Positive.	Positive.
	2. Pott's disease of spine, bronchopneumonia, and bronchiectasis.	2. Characteristic organisms.	Positive.	Positive.
14. Chiari,	Cerebellar abscess, myelitis, bronchiectasis (mixed infection).	Characteristic organisms.	Negative.	Negative.
15. Von Jaksch,	Cerebral abscess, meningitis, bronchiectasis.	Characteristic organisms.	Negative.	Negative.
16. Ucke,	1. Pulmonary abscess and pyema.	Characteristic organisms (sputum).		
	2. Pulmonary gangrene.	2. Characteristic organisms (sputum).		
	3. Pulmonary gangrene.	3. Characteristic organisms.		
	4. Pulmonary gangrene	4. Characteristic organisms.		
	5. Subphrenic abscess.	5. Characteristic organisms.		
	6. Noma.			
17. Musser & Gwyn,	Bronchopneumonia.	Characteristic organisms.	Negative.	Negative.
18. Musser, Gwyn, and Pearce,	Cerebral abscess.	Characteristic organisms.	Negative.	Negative.

DISCUSSION.

DR. FLEXNER: I would remind the society of a case of streptothrix infection of a human being, perhaps the first reported in this country, which I had the pleasure of describing to this society a few years ago. That case resembled tuberculosis, and would have been so regarded but for the micro-

scopic examination. It was a case of pneumonia seen in Dr. Osler's wards at the Johns Hopkins Hospital, and which came to autopsy while I was working at the hospital. There was extensive consolidation of the lung and beginning cavity-formation. There was also wide-spread tuberculosis of the peritoneal cavity. The organism was found on cover-slip preparations and belonged to the streptothrices. This case was coincident with one published in Germany and another in Japan, and two other cases have been reported from Dr. Prudden's laboratory.

Dr. Gwyn showed me his specimens, and in one case it was difficult to determine what the organism was. The brain lesion is interesting, inasmuch as the first of the whole group described by Eppinger a few years ago was in a brain abscess.

DR. ABBOTT: I have also encountered one of these organisms, and, as the previous speakers have said, the conditions produced by it are so like tuberculosis at first glance that one is excusable for mistaking the lesion. The animal, a rabbit, presented a large swelling about the angle of the jaw, with a caseous condition of a large part of one lung, and I was at first glance sure it was tuberculosis, but closer examination showed it to be a streptothrix infection.

THE BACTERIAL TOXINS.

By VICTOR C. VAUGHAN, M.D.,
OF ANN ARBOR, MICHIGAN.

Recognizing the fact that certain bacteria act harmfully on the animal organism by virtue of the chemical poisons which they elaborate, the manner of the formation of these poisons, their chemistry and their toxicologic effects become questions of great interest to students of etiology and pathology. It is supposable that bacteria elaborate these chemical poisons by a ferment-like or cleavage action on certain constituents of the animal body, notably the proteids, and that among the new chemical bodies thus formed the specific poisons are to be found. Moreover, it has been demonstrated that some bacteria, and among these certain pathogenic organisms, do produce soluble chemical ferments. Diastatic, inverting, proteolytic, steaptic, and other kinds of ferments have been found to be present among the products of the cellular activity of bacteria. Peptonizing organisms are frequently present in milk, and it has been suggested that milk poisons, galactotoxicons, may have their origin in the processes of proteolysis induced by these forms of bacteria. The bacillus of Asiatic cholera has been shown to be possessed of the power of elaborating both amylolytic and proteolytic ferments, and at least two investigators of good repute have satisfied themselves that they have found the specific toxin of this organism among the new bodies which result from the action of its peptonizing ferment. The lactic acid bacillus splits up lactose with the formation of acid, and there is probably no form of carbohydrate found in the higher plants which bacteria may not digest. Indeed, there is no organic substance, either animal or vegetable, which is capable of resisting under favorable conditions the destructive, analytic, cleavage action of bacteria. I mention these general facts, so well-known to all, in order to show how

reasonable it is to look for the specific bacterial toxins among the products of their cleavage action on complex organic substances. As soon as bacteriologists became convinced that pathogenic micro-organisms induce disease and death by the elaboration of chemical poisons, they began most energetically and enthusiastically to search for the specific toxins among the cleavage products resulting from bacterial activity. All the known toxicogenic germs have been grown in liquid culture media, and the chemical poisons have been sought for in the germ-free filtrates from porcelain filters and in cultures in which the living germ has been destroyed in some way. The results of these labors have by no means been in vain. They have given us much valuable knowledge concerning bacterial poisons. In many instances they have given us the crude toxins, and with these much information of value has been secured. Chemical immunity has been studied and antitoxins have been prepared and utilized with great credit to our profession and with greater benefit to mankind. But notwithstanding the value of the results obtained by researches guided by the theory that the specific bacterial toxins originate in their cleavage action, the theory is probably erroneous.

The following statement probably represents fairly well the opinion held by some bacteriologists concerning the formation of the specific bacterial toxins. At least they formulate the views held by the writer.

Histologically the bacterial cell consists of a cell membrane with protoplasmic contents. The membrane in many bacteria at least is of proteid composition. No one, so far as I know, possesses sufficient data to enable him to specify exactly the nature of the proteid of which the cell wall is composed, but that it is of a proteid character and does not consist of cellulose, or any form of carbohydrate, I am quite certain. This view does not exclude the possibility of the cell membrane in some bacteria being composed of a glycoproteid and yielding a carbohydrate on being decomposed with acids or alkalies. Physically, possibly chemically also, the cell membrane differs widely in different species, and possibly to a less marked extent in the same germ under different conditions of growth. In some bacteria the membrane is easily permeable both by its contents and by certain constituents of the medium in which the organism may be placed.

The specific toxin is formed within the cell and does not have its origin in the cleavage action of the cell directly or indirectly by similar action of a soluble ferment produced by the cell. The formation of the toxin is a synthetic and not an analytic process. The truth of this seems to be demonstrated by the fact that many of the pathogenic bacteria, and among these some of the most highly toxicogenic varieties, do multiply and elaborate their specific poisons in culture media, which contain only inorganic substances with small amounts of certain organic compounds of relatively simple constitution, such as Uschinky's fluid.

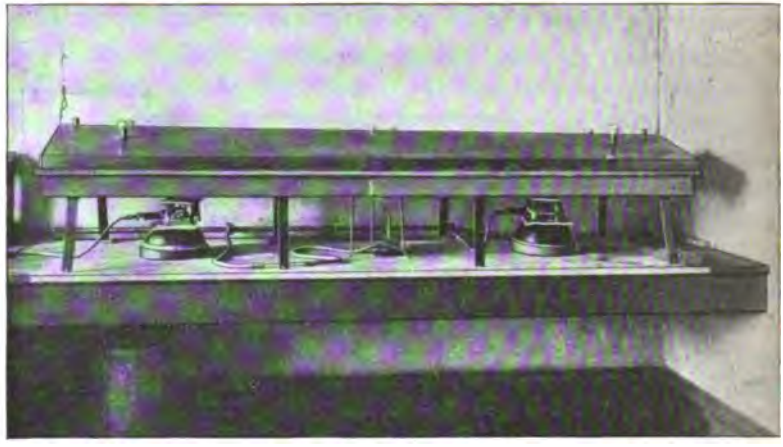
The formation of toxin is not one of the constant, essential, and invariable life-processes of the bacterial cell. In other words, the organism may grow and multiply abundantly without producing a specific toxin, and under certain untoward or unfavorable conditions the most highly virulent bacteria may vegetate luxuriantly without elaborating a toxin. The conditions which favor the production of toxins are known in cases of several bacteria. Some of these are temperature, oxygen supply, reaction of medium, etc.

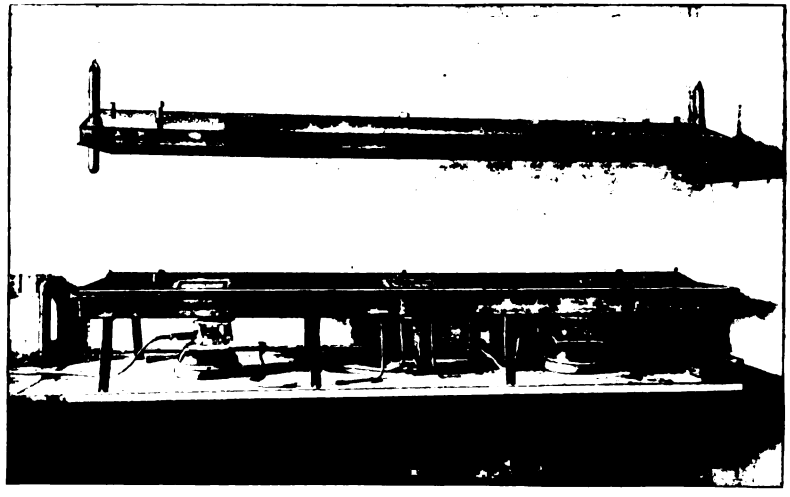
From this line of reasoning I conclude that the toxin is formed within the bacterial cell, but does not by any means constitute the sole constituent of the cell plasma.

With this theory formulated I have tried to study the toxins by obtaining a large amount of cell substance and endeavoring to extract the toxin from the cells. In this attempt I have met with many difficulties, some of which I have partially at least overcome, while others remain to be solved.

Naturally the first thing to be done is to obtain a large amount of cell substances practically free from the constituents of the medium on which or in which the germ is grown. As a medium, agar is well suited for this purpose. The bacterial growth can be washed or scraped from the surface of the agar quite free from the medium. The next thing to be done is to obtain large surfaces of agar. The best means at my command for this purpose when I began the work was the Roux flask, and by inoculating one hundred of these with the colon bacillus, allowing to grow from ten to fourteen days in the incubator, or from three to four weeks at room-temperature, and then washing off the growth with alcohol, I obtained a somewhat bulky and promising volume of germ substance; but when this was thoroughly

washed with alcohol and ether, dried at 100° and weighed I found that the total yield was, under the most favorable conditions, not more than three grams. It is true that I have frequently found





that the powder thus obtained kills guinea-pigs of two hundred grams weight in quantities of a fraction of a milligram, and with this crude toxin I have made some interesting observations; but in

order to study the chemistry of the toxin it was evident that I must secure the germ substance in larger quantity. Next I tried growing the colon bacillus in the ordinary moist chambers, used as Petri dishes, but with the greatest care many of these became contaminated. Finally, I devised for the growth of the germ on a large surface the following apparatus : A copper tank ten feet long, two feet wide, and four inches deep, with a trough around the edge one inch deep, is covered by a top of the same material. This tank is supported by an iron frame with legs ten inches high and the whole is placed on a table covered with galvanized iron. A tank two inches shorter and two inches narrower also provided with a trough around the edges and a cover sets in the larger one, and is supported two inches from the bottom of the larger one by iron bars extending from side to side. The bottom of the outer trough is filled with water, and the sealed trough of the outer tank is also filled with water. The sealed trough of the inner tank is filled with glycerin. Both lids are raised and let down by wire ropes passing through pulleys fastened in the ceiling. It is necessary that the tanks should be set perfectly level. Twenty liters of 2 per cent. agar is placed in the inner tank ; both lids are lowered, and with burners at full blast underneath the apparatus is a sterilizer. After repeated sterilization the upper lid is raised, and the agar inoculated by pouring through tubular openings in the top a liter of beef-tea culture of the germ. These openings are then sealed with wax and the outer lid lowered. Now, with gentle heat underneath the apparatus is an incubator.

With due care there is no contamination, and forty or more grams of dried pulverized germ substance can be obtained from each culture secured in this way.

So far my work has been chiefly confined to a study of the colon bacillus. The first experiments were made in 1897 with a colon germ obtained from cheese. Next I used cultures secured by a bacteriologic examination of a drinking water which was supposed to have caused several cases of typhoid fever, and, lastly, I have employed cultures obtained from normal feces. There are no recognizable differences in these cultures. In all the germ is a typical colon bacillus. It is non-motile, coagulates milk, reddens litmus, and responds to the indol reaction in beef-tea peptone cultures from

two to five days old. As a preliminary step the virulence of the culture is increased by passing the germ through animals.

The results of my work with the cell substances of the colon bacillus may be stated as follows:

1. The toxin is contained within the cell from which it does not, at least under ordinary conditions, diffuse into the culture medium.

This is shown by the following experiment: A beef-tea culture which had been grown for twenty-one days in the incubator was filtered through porcelain. Eight c.c. of the clear, sterile filtrate was injected intra-abdominally into a guinea-pig, weight 435 grams. The animal was restless for some time immediately after the injection, probably due to the volume of fluid used, but gave no other evidence of any effect of the injection.

As a control to this experiment, 0.25 c.c. of the same culture, unfiltered, injected into a guinea-pig of equal weight killed the animal within twelve hours.

It might be argued that these experiments do not show that the colon toxin is not insoluble in the beef-tea, but that the toxin, although insoluble, will not pass through a porcelain filter. This is shown not to be the case by the following experiment: An unweighed portion of dried bacterial cell substance was suspended in water, heated in the autoclave to 154° under two kilos of pressure, and filtered through porcelain. Four c.c. of the clear filtrate thus obtained was injected into the abdominal cavity of a guinea-pig. In thirty-six hours this animal died, and the postmortem findings were those usually observed after death from the crude toxin. This shows that the toxin of the colon bacillus, after being removed from the bacterial cell by superheated water, may be filtered through porcelain.

2. The toxin is not extracted from the cell by alcohol or ether.

I have repeatedly extracted the bacterial cells with both of these reagents at different temperatures, evaporated the extracts thus obtained, in vacuo, dissolved the residue in water, and injected these aqueous solutions into animals. No effect has followed this treatment. That extraction of the cell substance with alcohol or ether has no destructive action on the toxin is shown by the fact that the cell substance thus extracted does not lose any of its tox-

icity. Furthermore, it may be stated that these reagents even after prolonged boiling do not induce any visible alteration in the form or tinctorial properties of the germ. Traces of fat and coloring-matter are apparently the only substances extracted from the cells of this germ by alcohol or ether, and it is probable that all the coloring-matter and the greater part of the fat thus extracted come from the presence of traces of the agar on which the bacillus has been grown.

3. Very dilute alkalies do not extract the toxin from the unbroken cells.

This is shown by the following: One hundred mg. of germ substance, dried but not pulverized, was boiled in an open test-tube for five minutes. The germ substance was then separated from the supernatant fluid in a centrifuge, and was found to be still highly toxic, while the fluid was inert. However, after the dried cells have been finely ground by prolonged attrition in an agate mortar the toxin is, in part at least, soluble in weak alkalies.

4. The unbroken germs may be heated to a high temperature with water without destruction of the toxin.

Two hundred mg. of the germ substance was placed with 10 c.c. of water in a tube, which was then sealed and heated at 184° for thirty minutes. On opening the tube the milky content was found on microscopic examination to contain granular débris with a few unbroken cells. Portions of this heated substance injected into guinea-pigs caused death, and autopsy revealed the same lesions that are usually found in these animals after death from the colon toxin.

Another portion of the content of this heated tube was placed in a centrifuge and separated into a deposit and a supernatant milky fluid. Guinea-pigs were injected, some with the deposit and others with the fluid; both sets died. This shows that superheated water breaks up the cell wall.

5. Boiling with a 0.2 per cent. aqueous solution of hydrochloric acid has but little, if any, effect upon the germ cell or its contained toxin.

One hundred milligrams of the germ substance was boiled in an open test-tube with 10 c.c. of a 0.2 per cent. solution of hydrochloric acid. This induced no visible alteration of the bacterial cells as

seen through the microscope, and the injection of the germ substance thus treated, after neutralization, caused death in animals in the usual time and with the usual postmortem findings.

6. Heating the germ substance for an hour at the temperature of the water-bath with water containing from 1 to 5 per cent. of hydrochloric acid breaks up the cell wall and lessens but does not destroy the toxicity of the cell content. Prolonged heating may render the toxin inert.

Five hundred milligrams of germ substance was heated on the water-bath for one hour with 500 c.c. of a 5 per cent. solution of hydrochloric acid. I then decanted through a filter. The filtrate was clear and colorless, and gave no precipitate when dropped into absolute alcohol, but that the acid had dissolved some part of the substance is shown by the fact that the filtrate gave the biuret test.

The portion undissolved by the acid was dissolved in 100 c.c. of a dilute solution of sodium bicarbonate, and this was injected in guinea-pigs as follows:

No. 1	Weight	275	grams.	Received	10	c.c.
" 2	"	255	"	"	9	"
" 3	"	267	"	"	8	"
" 4	"	250	"	"	7	"
" 5	"	305	"	"	6	"
" 6	"	285	"	"	5	"
" 7	"	300	"	"	4	"
" 8	"	315	"	"	3	"
" 9	"	290	"	"	2	"
" 10	"	250	"	"	1	"

These injections were made at 6 P.M., February 5th. Nos. 1, 2, 5, 6, 7, 8, and 10 were found dead at 7 A.M., February 6th; No. 4, on the morning of February 8th; No. 3, on the morning of February 9th, and No. 9, on the morning of February 11th.

7. The toxin separated from the cell wall by digestion of the latter with hydrochloric acid and pepsin is markedly active.

I removed the germ growth from fifty Roux flasks, and extracted it with 96 per cent. alcohol at ordinary temperature as long as the alcohol took up coloring-matter. The germ substance was then collected upon a filter and the alcohol allowed to drain away; then the mass of germs was placed in a beaker and 1000 c.c. of 0.2 per cent. solution of hydrochloric acid and 0.5 gram of active pepsin added. The beaker with contents was allowed to stand for four

days in the incubator, the mixture being occasionally stirred. The undigested portion is found by microscopic examination to be amorphous, but still easily stained with methylene-blue. This was collected on a filter, washed thoroughly with 96 per cent. alcohol, dried to a constant weight at 100°, and pulverized. One hundred milligrams of this powder were shaken with 50 c.c. of water, with which it formed a colloidal body of acid reaction. On adding enough bicarbonate to render the mixture feebly alkaline, the substance dissolved to an opalescent fluid. This was sterilized by boiling over the naked flame and was injected into guinea-pigs:

No. 1	Weight 407 grams.	Received 16 mg. of toxin.
" 2	" 392 "	" 12 " "
" 3	" 320 "	" 10 " "
" 4	" 455 "	" 8 " "
" 5	" 417 "	" 6 " "
" 6	" 470 "	" 4 " "
" 7	" 442 "	" 2 " "
" 8	" 412 "	" 1 " "
" 9	" 432 "	" 1 " "
" 10	" 480 "	" 2 " "

Nos. 1, 2, and 3 died within six hours; Nos. 4, 5, 6, 7, and 10 within twelve hours, and Nos. 8 and 9 within twenty-four hours. One-fifth of a milligram of this toxin kills guinea-pigs of two hundred grams and less weight.

After death from this toxin there is usually, not always, considerable (from 2 to 10 c.c.) of serum in the peritoneal cavity. This is sterile if removed before postmortem infection takes place, and it has absolutely no germicidal action on the colon bacillus, as the following extract from my protocol-book shows :

" Every tube of exudate taken from the above-mentioned pigs proved to be sterile. This was shown by making beef-tea inoculations from each tube, all of which remained free from growth. I then tried the germicidal action of these exudates on the colon bacillus. A loop of a beef-tea culture of this germ was placed in a tube of beef-tea and then a loop of this dilution was added to a tube of the serum, and plates made from this at intervals.

Time . . .	5 min.	15 min.	30 min.	60 min.
Colonies . .	10	25	28	100

" This test, repeated several times, shows that the serum that collects in the abdominal cavity after fatal poisoning with the toxin

of the colon bacillus has no bactericidal action on this organism, but furnishes a medium on which it grows readily.

"This serum is not only without germicidal effect on the colon bacillus, but it fails to agglutinate this organism."

The amount of toxin present in the germ substance obtained in different harvests, even when the beds of agar have been planted with the same culture, seems to be very variable. Whether this is due to slight and unrecognized variations in the process of securing the dried germ substance, or to the development of more toxin in one growth than in another, I am not prepared to say with certainty, although I am inclined to the latter opinion. It is probable that slight variations in the reactions of the nutritive medium or in the temperature at which the growth is developed influence the amount of toxin formed. However, there is a much more interesting observation met with in my studies. With the same toxin individual animals show wide ranges of susceptibility, as will be shown by the following extract from the protocol.

The following injections were made at 5 P.M., March 25th:

No. of pig.	*Weight.*	*Mg. of toxin used.*	*Result.*
1	542	5	Died at 9 A. M. March 26.
2	560	4	Died at 9 P. M. March 25.
3	785	3	Died at 11.30 A. M. March 26.
4	712	2	Found dead April 1.
5	645	10	Died April 15.
6	520	2	Died at 12 P. M. March 25.
7	510	1	Found dead April 9.
8	225	0.5	Died at 11 P. M. March 26.
9	287	0.75	Remained well.
10	377	0.3	" "

It may be observed that Nos. 4, 5, and 7 did not die from the primary effects of the poison, and that No. 5 received more than three times as much toxin as did No. 3, which was a larger animal, and twenty times the amount that killed No. 8.

The following injections were made at 3.45, March 26th:

No. of pig.	*Weight.*	*Mg. of toxin used.*	*Result.*
1	540	20	Found dead at 7 A. M. March 27.
2	607	16	Died at 11.30 P. M. March 26.
3	557	12	Died at 8.50 P. M. March 26.
4	672	10	Died at 8.00 A. M. March 27.
5	482	10	Died at 12.00 M. March 26.
6	675	4	Still lives.
7	565	3	Died at 12.00 M. March 26.
8	577	3	Found dead at 7.00 A. M. March 2.
9	715	2	Found dead at 7.00 A. M. March 27.
10	572	2	Died at 1.00 A. M. March 27.

It may be seen that the only animal in this set that survived received twice as much as two of those that died.

The following injections were made at 4 P.M., March 27th:

No. of pig.	*Weight.*	*Mg. of toxin used.*	*Result.*
1	422	4	Found dead at 7.00 A. M. March 28.
2	467	6	" " " " " "
3	457	8	" " " " " "
4	385	2	Died at 11.00 A. M. March 29.
5	432	4	Found dead at 7.00 A. M. March 25.
6	437	4	Died at 7.30 A. M. March 25.
7	507	2	Found dead at 7.00 A. M. March 25.
8	495	4	Still lives.
9	392	1	Died at 11.00 A. M. March 29.
10	612	10	Died at 10.30 A. M. March 28.

The only animal in this lot that survived had four times the quantity of toxin received by No. 9, and twice as much as Nos. 4 and 7.

The effect of intra-abdominal and subcutaneous injections are practically the same, both in the amount necessary to kill and the pathologic changes found after death. There is but little or no local effect observed after subcutaneous injection, provided, of course, that a solution of neutral or feebly alkaline solution is used. It should be remembered that I have shown that the cell plasma of the colon bacillus is decidedly acid in reaction. Sometimes there is marked congestion of the subcutaneous bloodvessels, but this is as likely to occur after an intra-abdominal as after a subcutaneous injection. The bloodvessels of the mesentery are invariably congested. The degree of congestion varies in a general way with the size of the dose, and when this has been large there may be marked hemorrhages from these vessels. In most instances there is an exudate in the peritoneal cavity. This may consist of whole blood or of serum more or less colored with hemoglobin. The omentum is often much congested. In some instances there may be a gelatinous exudate formed over the coiled mass of the small intestine. The animals are usually quite hyperemic. The heart is in diastole, and generally filled with fluid blood.

When large doses are given to guinea-pigs either intra-abdominally or subcutaneously the temperature of the animal after two or more hours falls, and may go as low as 30°.

Immunity to both the toxin and the living germ can be secured by continuously increasing the dose of the toxin administered, but

great care is required, and in all my experiments in this direction the majority of the animals have died while undergoing the immunizing process.

There are many interesting problems in connection with this toxin which I do not yet feel able to discuss. If the toxin be confined within the cell wall, how is it set free when the whole germ, either living or dead, is introduced into an animal? If this is accomplished by phagocytic action, do the phagocytes destroy the toxin when they kill the germ? What is the chemistry of this toxin? Is it a definite compound, or is it composed of the many substances mentioned by Ehrlich in his theory concerning the constitution of toxins? Does the bacterial cell contain both a toxin and an immunizing body, or may this toxin be changed into an immunizing substance either by artificial means or within the animal body? These and other similar questions await further study. Although I have pushed my investigations along the lines here suggested further than is indicated in this paper, I do not feel that the knowledge obtained up to the present time is sufficiently accurate to satisfy myself or others, and I prefer not to indulge in theories. However, the fact that at least one of the bacterial toxins is a remarkably stable body, and can be obtained in the dry state and permanent form, justifies us in taking a somewhat more optimistic view concerning the probability of ascertaining the chemical composition of these bodies than that recently expressed by Brieger and accepted by Ehrlich.

HEMORRHAGE FROM A PYOTHORAX.

By A. JACOBI, M.D., LL.D.,
OF NEW YORK.

Maria C., aged seven years, born in the United States, of Italian parentage, was admitted to the Jacobi Ward of the Roosevelt Hospital, New York, October 29, 1900. The family history was negative; the personal history, according to the rather unintelligent parents, was good until present illness. The child was taken ill a month previous to admission; she felt languid, rather feverish, had no appetite, lost flesh, had some pain about right chest, and coughed occasionally; the temperature on admission was 102° F.; there was marked dulness over the right lung, lower lobe, up to the fourth or fifth rib; there was flatness over the base; the voice and breathing approached the bronchial near the apex, and were absent over the base; the respiration was 40; the pulse, 140; the appetite was good; sleep was fair.

Puncture on November 1st yielded pus.

Operation under chloroform November 2d. Five centimeters of the sixth rib, in front of and below the angle of the scapula, were removed. White and inoffensive pus flowed out readily to the amount of perhaps 500 c.cm., not mixed with blood. Thiersch's solution was injected; it returned with a little more pus, which was slightly colored with blood. All at once a large quantity of blood was discharged, which, when the irrigation was stopped, proved to be undiluted blood. It was clear it could not come from the intercostal artery, which was not touched. Full irrigation was again resorted to for a few seconds; the light being good, and the opening large, the blood was seen oozing in quantities from tufts disseminated over the pulmonary pleura, the costal not being within view. These tufts could easily be distinguished with the fingers, extended over a large surface, and were quite numerous, large and small, some being nearly a centimeter in diameter, others apparently not over the size of a pinhead. Altogether at least 250 c.cm. of blood were thus lost. The lung not expanding readily, the cavity was immediately filled with large quantities of sterile gauze, which was allowed to remain in place for two days. When it was removed some little fresh blood was seen to ooze from a few large granulations. Gauze in somewhat smaller quantities was introduced; it was removed after two more days, when no blood was found, with the exception of a few small clots swimming in pus. The cavity, which diminished in size, was again filled with gauze for

some days, until a drainage-tube could be safely inserted. At that time the pleural surface was no longer red, the granulations had shrunk so that the thickened membrane exhibited only some flat and occasionally rough elevations of a grayish-yellow color. A careful search for a malignant tumor had no results, nor was there a suspicion of tuberculosis[1] or of maceration and corrosion of the surface; and there was certainly no adhesion between the two pleuræ, the tearing of which could have given rise to some of the hemorrhage which took place.

Within a few days the temperature became normal and remained so with a few interruptions. The child's weight on October 29th was thirty-nine pounds seven ounces; on November 7th, thirty-eight pounds—the difference was apparently due to the pus and blood lost on November 2d; on the 14th, thirty-nine pounds ten ounces; 29th, forty-one pounds four ounces; January 9th, 1901, forty-seven pounds twelve ounces. A few days after she was discharged, the recovery being retarded by the slowness of the expansion of the lung, held down as it was by the thickened pleura.

Hemorrhages into the pleura may take place from rupture of an aneurysm, ulceration of the aorta, bleeding from the venæ cavæ, caries of the rib, penetrating wounds or contusions of the lungs, or thrombosis. F. W. Zahn, Geneva, described (*Virchow's Archiv*, 1885, vol. vii. p. 345) a case of bilateral hemorrhagic pleurisy following the thrombosis of the vena azygos. It was observed in an alcoholic coachman of thirty-two years and followed extensive trauma and inflammation of the inguinal region. In this case the pleurisy appears to have followed the hemorrhage.

Other causes are primary or secondary malignant tumors of the pleura. Even in those cases in which a copious hemorrhage into the pleura takes place, with no suspicion of malignancy or other adequate causation, the final history corrected the first impression.

In the *Transactions of the Clinical Society of London*, 1878, vol. xi. p. 136, Dr. W. N. Broadbent published a case of very rapid effusion and extravasation into the right pleural cavity of a man of seventy-six years. The amount of blood was very large, the whole cavity being filled. Two quarts of serum and blood were removed by paracentesis, and the patient recovered, so that the diagnosis of a malignant tumor was given up. But within eight months dyspnea returned and symptoms of malignancy made their appearance, and within a year he died.

[1] During the discussion of this case Dr. Osler asked whether some tissue had been removed from the tufts for examination. That was omitted on account of the extensive hemorrhage, which seemed to permit of no delay.

Hemorrhages may be caused by sepsis at any age, mainly in the newly born. Such hemorrhages, however, are mostly petechial.

In a *Thèse* of Lacaz-Duthiers there is a case, of Tardieu's, of pleural hemorrhage without inflammation which necessitated thoracocentesis. It occurred in a cachectic man with paralysis and cystitis.

Resembling the hematoma of the dura mater, a pleural hematoma is described by Mesnil and Netter. It is the result either of the rupture of newly formed bloodvessels or of diapedesis (Fraentzel). Andral (*Clin. Méd.*, 2d edition, p. 473) has the case of a man of forty whose right pleural cavity, as far as it was not obstructed by adhesions of the upper lobe to the costal pleura, was filled with blood which extravasated from the fibrinous deposits of the pleura.

Contrary to what is observed in the common form of hemorrhagic pleurisy, where the blood amounts rarely to more than 10 per cent., more or less genuine hemorrhage is observed in purpura hemorrhagica, scurvy, hemophilia, pernicious anemia, variola, leukocythemia, icterus gravis, chronic diffuse nephritis or interstitial hepatitis. Pleural hemorrhages in heart diseases are rarely copious.

In tuberculosis there is, as a rule, hemorrhagic pleurisy but no clear blood. Still, Henri Blumenthal has the case of a woman of sixty years who died with her pleural cavities filled with blood. He speaks of the presence of gray granulations which are evidently tubercles (*Thèse : sur les hémothorax non traumatiques*, 1868).

A case of pleural hemorrhage, from Nothnagel's Clinic, was reported by J. P. Crozer Griffith in *The Medical News* of August 1, 1885. It was not, as had been supposed, the result of a hemorrhagic diathesis but of miliary pleural tuberculosis.

My case was unique in my experience and furnished an additional cause of hemorrhage into the pleural cavity. Scanning the literature has not added to my knowledge on this special cause of bleeding. That is why I have asked a number of active surgeons in regard to it, and was told they had not seen its like. That is also why I claimed a very few minutes of your time to make this communication of a case in which the pleural abscess behaved to an unusual degree similarly to what may be observed in abscesses situated in looser tissues elsewhere, in which granulating tufts spring up from the surface with, occasionally, a very moderate tendency to bleed.

CYST OF THE OMENTUM.

By A. JACOBI, M.D., LL.D.,
OF NEW YORK.

Josephine C., aged seven years, born in the United States, of Italian parentage, was admitted to the Jacobi Ward of Roosevelt Hospital, October 10, 1900. Four years previously the abdomen began to swell, and the child lost flesh and looked out of health. The diagnosis of ascites, probably of tuberculous origin, was made by the chief of my clinic, Dr. F. Huber. He performed paracentesis and drew two quarts of a clear, slightly bloody serum. The swelling disappeared, and the child improved and appeared cured. After two years the swelling, with fluctuation over the whole abdominal cavity, returned; the child lost flesh, looked bad, and was again tapped by Dr. Huber, after which the health of the child improved. There was no history of cough or of bloody or other expectoration. In the spring of 1900 the abdomen filled again, with some impairment of the looks of the child. Still she was active and had good appetite, sleep, and strength. No cough, expectoration, or sweats. When she was admitted there was an occasional cough; there were many but small lymph-bodies palpable in the groins and axillæ, but there was no change in the respiration of either lung, but a very slight extensive dulness in the right axilla down to the liver. The body-weight was forty-seven pounds five ounces. The kidneys and urine were negative. Abdominal circumference over last rib, 69 cm. =28½ inches. Fluctuation universal in all directions.

October 22*d*. Three hundred c.cms. of a slightly bloody serum were withdrawn. The opening of the trocar then became obstructed, I thought, by intestinal coils, and the operation was interrupted.[1]

30*th*. The circumference was only twenty-three inches; it remained so until the middle of November, when it began to increase again. Body-weight on November 7th, forty pounds ten ounces; on the 14th, forty-one pounds and eight ounces. Neither the operation nor the subsequent absorption caused any change of temperature. On November 22d the patient was transferred for laparotomy to the surgical service of Dr. Weir.

The child was operated upon by Dr. R. F. Weir under chloroform anesthesia. The incision, two inches and a half in length, was made in the

[1] The fluid was examined, with negative result, for tubercle bacilli only.

median line and commenced from a point about an inch and a half above the umbilicus, and was directed upward. A very thin-walled multilocular cyst presented itself, which, when drawn out of the abdominal cavity, contained about two quarts of straw-colored fluid in its main cavity, and was found to be incorporated in and involved the greater part of the great omentum, the cyst narrowing off into two pedicles as it approached the stomach. These pedicles of the omentum were ligated and the cyst was easily removed. The contents were mostly lost.

Two days after the operation the temperature rose suddenly to 103.2° F., and the child began to cough. During the next nine days the temperature fluctuated between 100° and 104°, rising once to 104.4° F. No observation was recorded of the possible cause of the cough. It does not appear that the temperatures had anything to do with the wound, for recovery was complete. The abdominal wound healed by primary union, dressings were omitted on the eighteenth day after the operation, and the patient was discharged, cured, on December 30, 1900.

The upper part of the specimen consists of omentum, which is cut off in two places. The cyst is large, with a number of recesses communicating with the main cyst with mostly large openings, some of them from three to five centimeters in diameter. It is covered with large and anastomosing bloodvessels and lymph-vessels, running in thick solid tissue. Between these masses of thicker tissue the wall of the cyst is quite thin and translucent. The cyst wall consists of several tissues, unstriped muscular fibers, fat, and fibrous tissue, in layers of different thicknesses, traversed by enlarged blood-capillaries and lymph-capillaries. It has on both sides, both externally and internally, a lining of endothelium, such as lines bloodvessels and lymph-vessels. The gelatinous contents are finely granulated; they consist of coagulated serum, with multinuclear and eosinic forms of leukocytes, endothelial cells, and a few red blood-cells. Staining with Weigert's method proves the absence of fibrin.

Reference to cysts of the omentum is not quite infrequent, but mostly indefinite. Thus, I. H. Fruitnight says in the *American Text-book of the Diseases of Children*, Philadelphia, 1894, p. 586: "Cysts are met with not infrequently. They are usually dermoid in nature, though simple serous cysts are encountered." The *American Text-book of Surgery*, 1892, p. 743, has the following only: "Cysts between the peritoneal layers of the mesentery, containing serum or a sanguineous fluid, have been successfully removed by operative treatment. Chylous cysts have sometimes the size of a head." In his discussion on acute sarcoma of the omentum, Koenig says that between the nodules and nodes ascitic fluid may be found in cysts, and adds that in operations for hernia Richter and Dieffenbach found an

additional membrane. Cutting into it they got into a cavity, the result of inflammation, filled with clear or bloody serum, with a portion of omentum.

The differential diagnosis from an ovarian cyst may be easy in those cases in which the mesenteric cyst is found to be high above the pelvis, bulging, and supplied with a distinctly perceptible part of the mesentery, which appears to act as a pedicle. But these peculiarities are rare, and when the walls are thin and the size is large a unilocular cyst may easily be and has been mistaken for ascites.

Dermoid and hydatid cysts and tuberculous tumors should be excluded from our consideration. They form a large part of the literature collected by Dowd under sixty-nine headings. With the exception of a few cases of hematoma and abscess, nothing remains but chylous and serous cysts. Nearly all of them, perhaps all, are of lymphatic origin, and result either from dilatation of lymph-veins or from a cystic degeneration of lymph-bodies, such as Rokitansky described at an early time (*Lehrbuch der Anatomie*, p. 677). Of the first variety, Weichselbaum reported a case (Virchow's *Archiv*, xiv.), and Sabourin and Le Dentu another (*Bulletins de la Société d'Anatomie*, 1876, p. 339). The contents were chyle. The same should be said of the second variety, as long as the case is of recent origin, as in the cases of Werth (*Archiv für Gynäkologie*, 1880) and of Duerkler (*Bulletins de l'Académie de Médecine*, 1880). Werth's case is that of an omental cyst the size of a child's head. It was described in the *Archiv für Gynäkologie*, 1882, vol. xix. p. 321. It rose from a segment of the mesentery belonging to the small intestine. Its contents were rather thick, whitish, and looked like chalk suspended in water, and contained albuminous and fatty detritus, but no formed elements, particularly no epithelia which would permit one to trace the origin to a tissue with epithelium. The walls consisted mainly of connective tissue, coarse and fine, the latter with small spherical cells in the intestines, of pronounced lymphatic character. This is why the cyst must not be taken for an actual neoplasm, but is a cystoid degeneration of a lymph-node which was alleged by Rokitansky as the source of such degeneration. The latter can best be explained by a primary obliteration of vasa efferentia, which, the entrance of chyle not being impeded, must lead to retention and dilatation.

A similar cyst was described by Eppinger (*Prager Vierteljahrsschrift*, 1873). His description tallies perfectly with the above, and does not justify his opinion, according to which his specimen is dermoid. The latter, however, is sometimes found, and is mentioned by Klebs (*Handbuch der path. Anat.*, vol. i. p. 331).

When cysts are of longer duration their contents become altered, greenish, yellowish. Péan quotes Ducarsel (*Bulletins de la Société d'Anatomie*, 1848), who found in the multiple lymph-body cyst of a boy of four years a few recesses filled with chyle, and others with a serous fluid. Rokitansky made the same observation in a man of fifty-three. In all of these the wall was thick, with the structure of the lymphatic system and without epithelia in the interior. Thus it appears probable that the serous cysts should be considered to be chylous cysts of long duration. The number of observations is limited. In his remarks on operative treatment, Péan mentions sixteen cases of serous and fourteen of chylous cysts. In that number he is probably mistaken.

All of the three cystic tumors in Péan's personal observation exhibit a peculiarity which seems to deny them the diagnosis of a genuine mesenteric cyst. For they were attached to the posterior wall of the abdomen and appear to have got between the layers of the omentum secondarily only during their growth and the consecutive opening of the omentum. They seem to be of retroperitoneal origin. If that is so, or, rather, as that is so, his strenuous objection to extirpation is not justified, nor is his preference for opening and drainage.

Mr. Albon Doran exhibited for Dr. Bantock to the Obstetrical Society of London (*Transactions*, 1882, vol. xxiii.) a large thick-walled single cyst, removed from a woman, fifty-eight years old. Its symptoms always resembled those of an ovarian cyst; it once ruptured and filled again, and several times it was tapped, dark serous fluid being removed. The great omentum was normal from the greater curvature of the stomach to its usual adherence to the transverse colon, but could be traced as a thickened and calcified sheet on the top of the cyst, which proved to be entirely within the omentum. One fold of the latter completely separated the tumor from the normal pelvic organs. The tumor was partly adherent to this fold of mesentery and to the transverse mesocolon.

Mr. Doran also exhibited a Hunterian specimen (No. 1109, Path.

Series, Museum, R. C. S.) of a small cyst in the folds of the great omentum.

Mr. N. Terry Marsh and Mr. Keith Monsarrat publish (*British Medical Journal*, March 2, 1901) a case of multilocular cystoma of the omentum which was removed from a female child three years and five months old. The tumor consisted of a large thin-walled cyst, capable of containing ten pints, and a number of independent smaller cysts varying in capacity from eight ounces to one dram. In some of the smaller cysts the fluid was a clear serum, but in all the larger ones it was deeply tinged with blood. The walls of the cysts, and particularly those of the large one, had numerous anastomosing vessels; they were large and thin-walled in the large cyst, smaller and firmer, and more firmly embedded in connective tissue in the smaller cysts. All of the cysts resembled each other histologically. Externally they carried an endothelial covering, internally a coat of fine connective tissue containing numerous blood-channels.

The several layers of the omentum were not traceable in the cyst walls; that circumstance, the presence of numerous large bloodvessels, and the early appearance of the tumefaction point to a fetal inflammatory process, for the abdomen was noticed to be considerably enlarged when the child was one year and four months old. At the age of one year and eight months the abdomen measured 23½ inches. There were general fluctuation and dulness. Five weeks after admission the first puncture was made, the second nine months later; nine months after this the third; two months and a half afterward the fourth and last. Soon afterward laparotomy was performed. There were two attachments, one in the right iliac fossa, the other consisted of the omental attachment to the greater curvature of the stomach, forming a broad pedicle for the whole mass. Recovery was complete.

In the *Report of the Proceedings of the Pathological Society of London*, 1851–52, p. 374, Dr. W. T. Gairdner describes a cyst that was "found beneath the anterior layer of the greater omentum in a woman. It consisted of a highly transparent closed sac, between three and four feet in length and from a half to one and a half inches in breadth, having a lobulated appearance externally, like that of the distended colon, but in no part subdivided by any approach to complete septa. The sac was fed by numerous vessels running within

the omentum and rarefying over it in every part. The fluid in the sac was a transparent, colorless serum, containing numerous flocculi. No parasite or ova were discovered. In the same woman were found in the cellular tissue of both groins a cluster of globular cysts of the ordinary type, similar cysts in the large uterine fibroid, and a globular cyst of the size of a bean in the pineal gland."

Thornton (*British Medical Journal*, 1882, ii. p. 1243) describes two cases of small omental cysts, both of which were found accidentally during operations on a papillomatous and a sarcomatous ovary. One was very small, multilocular, at the lower part of the omentum; the other, of the size of a small cocoanut, had a thick whitish wall and a puckered lining. It was attached to the omentum by a heavy vascular pedicle under the edge of the liver.

Dr. Gooding has a case of omental cyst (*Lancet*, February 12, 1887). It had the size of a fetal head, was without a pedicle, and was embedded in the omental folds.

Spencer Wells operated on a child of four years (*British Medical Journal*, June 14, 1890).

Dr. Buckley (*British Medical Journal*, May 16, 1885) has the case of a cyst with thick walls which contained about a quart of fluid, in which were found cholesterin and fat, beside "compound granular débris."

In William Osler's *Lectures on the Diagnosis of Abdominal Tumors*, Case L., on page 123, is that of a cyst of the mesentery of the last twelve or eighteen inches of the ileum; before removal it was suspected to belong either to the omentum or to the pancreas. The first tapping yielded a bloody fluid. During apparently good health the cyst filled repeatedly, nor was the health ever disturbed by or after the tapping. In the fluid cholesterin was found.

Altogether the number of uncomplicated and genuine omental cysts is small. Circumspection and careful acumen had to be called in to make the diagnosis in many cases. Thus, W. Joseph Hearn, while quoting a case of Schwartzenberger's, that of a true lymph cyst in a girl of four years, reports the case of a complex hydatid cyst of the omentum (*Annals of Surgery*, June, 1897). It was observed in and removed successfully from a boy of eight years, who weighed before the operation ninety-three and one-half pounds; two weeks after, forty-nine pounds. The abdomen was found large at

birth, diminished in size after six weeks, remained comfortable six years, and then grew rapidly until the abdomen had a circumference of 44 inches, and the distance from the ensiform process to the pubes amounted to twenty-five inches. Two aspirations yielded a small quantity of a brown fluid. Laparotomy removed the whole hydatid mass, which was taken out in compartments and was found to have its origin in the folds of the omentum, below the margin of the transverse colon.

It will always be difficult to decide whether such hydatids occur primarily in the omentum or, as Schwartzenberger maintains, have their primary seat in the liver.

A case of Doran's (*Obstetrical Transactions*, vol. xxiii. p. 561) and another of Ormsby's (*British Medical Journal*, 1883, i. p. 578) originated in the ovaries.

A large intestinal cyst, 22 cm. long, 14 broad, and 10 deep, was observed by C. Hennig (*Centralblatt für Gynäkologie*, 1880, No. 17, p. 398). Delivery was instrumental, very difficult, the child dead (lacerated). The sac contained still 100 c.cm. of a pretty clear, slightly red, and viscid fluid, which betrays its intestinal origin. Weigert found cylindrical epithelia on the wall and in the fluid and intestinal follicles in the wall. In the same child there was a cyst, of the size of a plum, covered with cylindrical epithelium, on the anterior wall of the third, fourth, and fifth cervical vertebra (branchial, probably).

Dr. W. Howship Dickinson describes (*Transactions of the Pathological Society of London*, 1871, vol. xxii. p. 296) a mesenteric tumor that occurred in a female child of two years. It was first noticed when the infant was between three and four months old. When the child died she weighed sixteen pounds. The tumor, together with the left kidney and a small portion of small intestine, weighed two pounds five and a half ounces. It nearly filled the left half of the cavity; in front of it lay the transverse colon and the cecum above, and a coil of adherent small intestine below. It consisted in its great bulk of ordinary connective tissue studded with true fat, in which there was found cartilage, bone, and many cysts, in which ciliated epithelium and plenty of mucoid masses were found.

This teratoma should not be considered among the serous cysts under consideration.

In addition to the serous, the dermoid, and those cysts which result from cystoid degeneration of lymph-bodies, Roth (Virchow's *Archiv*, vol. lxxxvi.) describes an enterocystoma which is congenital and due to the dilatation of the omphalo-mesenteric duct caused by obliteration.

Of cysts of the pancreas, Oser collected 134 cases. They are either (1) retention cysts (by inflammation, or compression of the pancreatic duct, or catarrhal inflammation, or concrements or neoplasms mainly in the head of the gland), or (2) proliferation cysts depending on adenoma, epithelioma, or carcinoma of the tissue, or (3) apoplectic (A. Russow, *Jahrb. f. Kind.*, vol. liii. p. 345).

DISCUSSION.

DR. KINNICUTT: An exceptional observation concerning a hemorrhagic effusion in the pleural cavity in the absence of the causes Dr. Jacobi has described should be accepted with some doubt; nevertheless, it seems to me such a case may be of interest. During the past winter a patient was admitted into my service in the Presbyterian Hospital suffering with acute lobar pneumonia, and two days after defervescence there were signs of effusion in the pleural cavity. Aspiration was practised, and the effusion was found to be almost if not quite pure blood. Three or four days later paracentesis was again performed and a simple serosanguinolent fluid obtained. A week later the fluid obtained was serous. The interesting points were that the pneumococcus was obtained from the serosanguinolent fluid from the sac; and the subsequent history of the patient up to the present time would indicate that it was a tuberculosis or rather a mixed infection. He has recovered and the lungs are entirely normal.

DR. HENRY: Tuberculosis has been referred to as though it was a cause of hemorrhagic pleurisy. Considering the fact that the majority of cases of pleurisy are tubercular, and that hemorrhagic pleurisy is extremely rare, I doubt very much whether there is any causative relation. In fact, the only cases of hemorrhagic pleurisy that have come under my observation have been associated with scorbutus. I reported a number of cases of scorbutus some years ago, in one of which there was hemorrhagic pleurisy. I have never seen hemorrhage into the pleural sac in connection with tuberculosis, and I have been teaching for some time past that the idea that a hemorrhagic pleural effusion is more likely to be caused by tuberculosis than by anything else is a delusion.

DR. PEABODY: As bearing upon this point it seems to me that cases are not very uncommon in which we find hemorrhagic pleurisy that subsequently get well. Whether they have a tuberculous pleurisy or not, of course, remains undetermined as long as they live and do not develop tuberculous symptoms; but we may have a large amount of blood effused into the pleural cavity in a person who is suffering apparently only with pleurisy. I have under observation now a man who is apparently well who three times within the past six weeks has required tapping, and on each occasion the fluid has been very bloody. I should be like Dr. Henry, somewhat skeptical as to the belief that this is necessarily of tubercular origin. It certainly has happened to me a number of times to have patients with only the history of ordinary pleural effusion, with large amounts of blood, get entirely well, and so I disregard the old view that they must have a neoplasm or tuberculosis, believing that blood in the pleural cavity may arise from other causes.

DR. SHATTUCK: I quite agree with Dr. Peabody that cases of hemorrhagic pleurisy do occur and get well, but not with his conclusion that therefore they are not tuberculous. The fact that they recover does not prove that they are not of tuberculous origin. I recall the case of a physician in Boston, the subject of great deformity from an old Pott's disease, who, late in life, developed hemorrhagic pleural effusion. He got entirely well, and remained so for several years after.

DR. HENRY: It is a well-known fact that tuberculosis of the serous membranes is more benign than in other tissues of the body. The point I made was that the vast majority of cases of pleurisy are tuberculous, while hemorrhagic pleurisy is extremely rare, and that consequently there can be no causative relation between them.

DR. KINNICUTT: I think Dr. Henry will admit that in tuberculous peritonitis the effusion is very different from that of the pleural effusion.

DR. OSLER: It is only in one variety of tuberculous pleurisy that we are apt to have hemorrhage. If he will look over the postmortems of any hospital, Dr. Henry will find his statement negatived by the presence of a number of cases of pleurisy with hemorrhage, but it is always the fresh tubercles surrounded by new vessels that bleed freely. It is the terminal form that is hemorrhagic.

DR. JACOBI: With the question of hemorrhagic pleurisy I had nothing to do. This was not a case of hemorrhagic pleurisy, but a hemorrhage in a case of pyothorax. When incision was made there came clear pus, and following that came clear blood. As the spots where the blood came from were washed I saw well-defined tufts, from which the blood was flowing or oozing. The cavity was packed with gauze, and after the first few days the

healing process was uninterrupted. I asked several surgeons about their experience in the matter, and they said they had not seen such a case. That is the only reason why I had the courage to communicate the case here. It shows an additional reason why hemorrhage may occur into the pleural cavity. All other reasons for hemorrhage are certainly well enough known, and I did not refer to them, except fragmentarily.

DR. OSLER: Were those little vegetations removed and examined for tubercle?

DR. JACOBI: No; I was in too much of a hurry to stop the bleeding. I must say that might have been done, but we were so shocked by the sudden hemorrhage that we only thought of stopping it. Still, it should be said that if we had an abscess in other parts of the body we should not be astonished at all by granulations springing up with hemorrhages as soon as the pressure on the sponge-like tissue is relieved. I will add that the child is in perfect health.

A CASE OF INDIGOURIA.

REPORTED BY A. McPHEDRAN, M.D.,
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AND
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THE presence of indigo-blue in the freshly-passed urine is of such great rarity and its significance so little more than that of potassium indoxyl sulphate that it can only be looked upon as a medical curiosity, and it is as such that attention is called to the following case:

Mr. G. E., aged twenty-four years, a fairly nourished man, of small build, looking old for his years by reason of his sallowness and falling hair, came complaining of a general weakness, heaviness of limbs, palpitation, dull headaches, and inaptitude to work. He is of sedentary habits, smokes very heavily, appetite is indifferent, but at the same time eating well, irregular as to his meals, and eating with such haste that he really bolts his food. Bowels are regular as a rule.

On examination few or no objective signs were to be found, the stomach being slightly prolapsed had good motive power, and its secretion was normal or slightly hyperacid. In an attempt to empty the stomach after an ordinary meal the tube was blocked with large masses of unmasticated meat.

No disturbance of the genito-urinary tract could be made out, but on passing urine for examination it at once attracted attention by reason of its turbidity and extremely bluish-green color. He then stated that some weeks before he had passed urine nearly as blue. This coloration could not be due to a drug, as none had been taken for a considerable length of time, nor was there a possibility of deception.

On examination this sample gave the following results: Color, bluish-green; transparency, turbid; reaction, slightly acid to litmus-paper; specific gravity, 1029; albumin, none; sugar, none; urates, excessive for the sample, quantity for the day being unknown.

Microscopic Examination. Amorphous and spherical urates, most of which were tinted various shades of green and blue. Separate particles of blue pigment in irregular masses and in amorphous form, not soluble on warming.

Bacteria. A few short bacilli apparently of the one variety, not staining by Gram's method; no cultures made. Among the ordinary deposits of urine no other abnormal constituents could be made out.

The pigment was readily extracted from the urine by chloroform, giving a solution which varied from a light green to a bright blue, according to concentration. On evaporation of the extract a bright blue pigment remained, which sublimed with a tinted vapor and condensed on the surfaces beyond the typical crystals of indigo-blue. The pigment was insoluble in water, ethyl alcohol, dilute acids, but readily soluble in chloroform, ether, carbolic acid, and hot methyl alcohol. With strong nitric acid it gave a yellowish-colored solution, while with sulphuric acid, at first a greenish solution quickly decolorizing.

After twice extracting the urine with ether, it was subjected to hydrochloric acid and potassium chlorate for the presence of the indoxyl sulphate, and again extracted with ether. Only the faintest trace of a bluish-green color resulted, and this, in all likelihood, was due to the imperfect primary extractions. As no more such pigmented urine was passed, a further study of the chemical nature of the pigment had to be given up; that it was indigo-blue cannot be doubted, not only because of its reactions but also for the reason that the patient usually passed yellowish-brown urine strong in indican, a sample of which, obtained a few days after the passing of the blue urine, gave the following results on examination: Color, yellowish-brown; reaction, acid; specific gravity, 1024; transparency, quite clear when passed, but rapidly becoming turbid by the falling out of amorphous urates. Urates were found to be excessive for the sample. Vigorous shaking, after the addition of a few drops of strong hydrochloric acid, produced a greenish coloration, the pigment being readily extracted with ether and chloroform. No other abnormality was found by chemical or microscopic examination.

The literature on the subject of indigo-pigments occurring in the urine is of much greater volume than one would have expected. From Braconnet's time, and even before, many cases are referred to or recorded of a blue or bluish-black pigment occurring in the urine, especially in connection with severe intestinal disorders such as Asiatic cholera and typhus. Of recent years, however, it has not attracted attention, partly due to the changed treatment of intestinal disorders, and more particularly because the examination of urine does not include the setting aside of urine for sedimentation, thus permitting of advanced decomposition with the accompanying oxidation of the potassium indoxyl sulphate.

The occurrence of the indigo-pigments in the urine as passed, however, is a condition seldom referred to or recorded. Ord, Roberts, Prout, Simon, Gilchrist, Kornblume, Dickinson, Robin, Beale, and

others mention cases, and all of the one class, that in which decomposition of urine occurred within the bladder, as evidenced by the signs and symptoms of cystitis and the passing of ammoniac and offensive urine.

The only cases I have been able to find in the literature at my disposal which resemble this case are those reported by Phillips, Wheaton, and Hughes.

That of Phillips was in a young married woman, who during six years' observation had for three periods of two weeks each passed urine of a greenish-brown to cobalt-blue color. This color was found to be due to indigo-blue. The general tone of the report would lead one to believe that there was no cystitis or marked decomposition of urine within the bladder, but it is not definitely so stated, nor is there a report of the chemical and the microscopic findings.

Wheaton's case is merely the mention of the passing of blue urine for a few hours by an hysteric woman.

The case cited by Hughes can hardly be classed with these cases, as it was assumed that urine passed during the night could not have changed in color by the morning.

I mention this case because the patient, according to the history, was just convalescent after typhoid fever, for it is in connection with such cases as are suffering from typhoid, typhus, Asiatic cholera, and intestinal obstruction, etc., that so many references as to the occurrence of indigo-pigments in the urine are made, and that without stating whether the urine was examined fresh or not.

From the work done on the antecedent of indigo-pigment, the potassium indoxyl sulphate, it is found that the absorption of indol, the product of albuminoid putrefaction, leads to indoxyl formation, and this combined in the form of potassium indoxyl sulphate is the antecedent of the indigo-pigment. These steps are brought about by oxidation. In the above diseases not only is the indol production frequently great, but the conditions for transmission to the general system are at their best. The indol apparently is transformed principally in the liver to the indoxyl form, and then to the potassium indoxyl sulphate, the final stage to the pigment usually occurring during decomposition after passage of the urine.

In such diseases it is known that the urine frequently contains large numbers of bacteria, not only of the specific form but bacilli of the colon

group, and others. In fact, bacteria are found comparatively frequent in the urine of individuals who are to all appearance in good health. The occurrence of these bacteria does not necessitate any marked decomposition or any appreciable signs or symptoms of irritation throughout the urinary tract. Now it is just possible that certain forms of bacteria, or bacteria under certain conditions, should bring about the oxidation of the potassium indoxyl sulphate to indigo without otherwise causing noticeable changes.

In the present case, if this explanation were accepted, we are at once confronted by the small number of bacilli found, the number being so few that it is hardly conceivable that they had any influence in the process. If they had no such influence we surely must look further back for the completion of the oxidation—to the portal system and liver, where the greater steps are usually carried out, or even back to the intestine, where the indol itself is produced.

HEMOLYSIS.

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Introductory. In the Transactions[1] of this Association of 1898 a remark of mine is published in which I refer briefly to some experiments I made to determine the modifying influence of the peritoneal cavity upon the deleterious effect of alien blood. According to Hamburger,[2] salt solutions or serous fluids of an osmotic pressure, differing from that of the blood of the animal—be they hypertonic or hypotonic—when introduced into the peritoneal cavity of an animal, assume after a while the osmotic pressure peculiar to the blood-serum of their host. This fact suggested to me the possibility that alien blood, too, might acquire a degree of adaptability to the new species by a preliminary stay in the peritoneal cavity of that species. To test this hypothesis I introduced fresh defibrinated bull's blood into the peritoneal cavity of a rabbit, left it there for three hours, removed it, and strained it. Blood thus prepared, when introduced through the jugular vein into the circulation of a normal rabbit, proved to be less harmful than unprepared bull's blood. Recently I have taken up this problem again, but studied it in the test-tube by the precise quantitative methods now in vogue in the recent marvellous studies of immunity and hemolysis. The primary object of this paper is the communication of the results of my recent studies. However, since the entire subject of hemolysis, as it has been developed in the biologic investigations of the last two or three years, is of such immense importance, it was suggested to me to present also a review of the recent hemolytic studies. This suggestion is the more justified, as there is in the medical literature of this country, at least so far as I know,

neither an original contribution to, nor a collective presentation of, this fascinating subject.* Acting on this suggestion, I shall, therefore, attempt to present a general review of the recent studies in hemolysis before giving the results of my own studies.

NORMAL HEMOLYSIS. Hemolysis means in general the solution of blood. The term, however, is now chiefly employed to designate the separation of the hemoglobin from the stromata of the red blood-corpuscles. This end can be attained by a great number of different agents. In the present article, however, we shall, in conformity with other writers on this subject, deal only with biologic agents, the foremost of which is alien blood or alien serum.

The early attempts at transfusion of animal blood into man showed that the normal blood of one animal is often detrimental to another animal. The fact was recognized quite early[3] that the serum of one animal can dissolve the erythrocytes of another animal. Even the agglutinating effect of alien serum was recognized quite long ago,[4,5] although it must be admitted that its importance was not understood until the recent advent of the knowledge of bacterial agglutination, when the fact of hemo-agglutination was rediscovered some six years ago by Bordet.[6] How dangerous, however, alien serum may be was only recently demonstrated by the discovery by A. Mosso[7] of the extreme poisonous effect of eel's serum; one kilogram of a mammal is killed by an intravenous introduction of 0.1 c.c. of eel's serum within three to four minutes. This serum is extremely hemolytic, as a trace of it rapidly dissolves mammalian erythrocytes in the test-tube.

Recent investigations have brought to light hemolytic properties in a number of other biologic products. Cobra venom and some other snake poisons possess hemolytic properties. Ehrlich[8] discovered that the tetanus toxin contains a hemolytic agent—the tetanolysin. Bulloch and Hunter[9] describe the hemolytic effect of filtered pyocyaneus cultures. Neisser and Wechsberg[10] discovered staphylolysin. Kobert[11] discovered the agglutinating effects of the four vegetable poisons—abrin, ricin, crotin, and robinin. Crotin exerts also a hemolytic influence upon the blood of certain animals.

The development of the method of studying the hemolytic effects of

* Since reading this paper I find that the literature on this subject is connectedly abstracted by Ludvig Hektoen in his excellent report on "Pathology," in Progressive Medicine, 1901, vol. i.

alien serum quantitatively in the test-tube was undoubtedly one of the most important factors in the rapid progress which has been recently made in the studies of hemolysis and allied subjects. However, the all-dominating point in this new field of extremely important and interesting investigations was the discovery of the so-called hemolysis by immunization about three years ago. This discovery is so closely interwoven with the recent development of our knowledge of bacterial immunity that we shall devote a few remarks to the latter subject.

BACTERIOLYSIS. In the first period of the new bacteriologic era infection meant invasion of bacteria, and immunization was accomplished in a general way by inoculation with bacteria. After the toxins were discovered, followed soon by the marvellous successes of active and passive antitoxic immunizations — to mention only the toxins and antitoxins of diphtheria and tetanus, or ricin and antiricin, abrin and antiabrin—the opinion became prevalent that all immunizations are probably of an antitoxic nature, and so the bacterium or the cell in general became less conspicuous. By the excellent studies of Richard Pfeiffer and his coworkers at about the middle of the last decade it was, however, established that there is a distinct and specific antimicrobic immunization which does not protect against the evil effects of the toxins. The sera of animals immunized against cholera and typhoid do not protect against the toxins of the bacteria in question, but are distinctly bactericidal. Pfeiffer found further that this bactericidal process has a morphologic aspect and is accessible to ocular observation. When, for instance, cholera vibrios were brought into the peritoneal cavity of a guinea-pig which contained serum of an animal immunized against cholera, the vibrios broke down into granula and soon dissolved entirely. The process, which is termed bacteriolysis, is extracellular (is therefore not phagocytic) and is distinctly specific; that is, the immune serum of cholera dissolves only cholera vibrios and no other bacteria. Gruber soon discovered another specific morphologic effect of the immune sera. Previous to their dissolution the bacteria often gather into clumps or masses. This is the phenomenon of "agglutination," which has become so widely known in its practical application in the diagnosis of typhoid. The phenomena of bacteriolysis and bacterial agglutination are independent of one another, and are, it must be said again, distinctly specific. Thus it has been established that there are two

distinctly different immunization processes: immunization against bacteria and immunization against their toxins, or as some toxins, like ricin, abrin, crotin, etc., are not the products of bacteria, we may express the broader conception by the term immunization against foreign cells and immunization against their toxic products.

This conception of immunization against foreign cells apparently prepared the minds of the investigators for the studies which followed. While the lively discussion over bacterial agglutination was going on, Bordet,[12] as mentioned above, rediscovered the agglutination of the red cells by alien serum. This, in conjunction with the already well-known lytic effect of serum of one animal upon the red blood-corpuscles of another animal, brought out the parallelism between hemolysis and hemo-agglutination on the one hand, and bacteriolysis and bacterial agglutination on the other hand. The effects of alien serum are also specific, as not every serum affects the red cells of all the animals, but serum of a certain species is hemolytic or agglutinative for the erythrocytes of a certain other species of animal. Another point which is common to both processes is that heating to 55° C. for half an hour deprives immune serum of its bacteriolytic property and deprives also the alien serum of its hemolytic action. When, now, in view of the many points which the relations of immune serum to bacteria have in common with the relations of alien serum to erythrocytes, and when, further, the experiments of Belfanti and Carbone brought out the fact that the serum of animals in which rabbit's blood has been injected is fatal to rabbits, the way was prepared for the last conclusion from these parallelisms, viz., that it ought to be possible to immunize against the red cells, just as it is possible to immunize against the bacterial cells. This explains how it came about that three investigators, independently of one another, have purposefully planned the discovery of hemolysis by immunization. The investigators were Bordet[12] in Paris, von Dungern[13] in Freiburg, and Karl Landsteiner[14] in Vienna. Bordet, whose publication of this discovery appeared a little ahead of that of the other investigators, has since followed up this subject with great ingenuity.

Hemolysis by Immunization. Now, what is hemolysis by immunization? Let us illustrate it by one of the experiments of Bordet. The normal serum of the guinea-pig has very little or no effect upon the red blood-corpuscles of the rabbit; even when brought together

and kept in the thermostat at 37° C. for many hours. If, however, a guinea-pig is treated several times at different intervals by subcutaneous or intraperitoneal injections of rabbit's blood, the serum of this guinea-pig acquires the capacity of dissolving the red cells of the rabbit with great rapidity, just as the serum of an animal which has been treated by bacterial injection dissolves such bacteria. This acquired hemolysis is specific. The serum of a guinea-pig immunized by rabbit's blood dissolves rapidly only the cells of rabbits, while it retains its normal indifferent behavior toward the red cells of other animals. The serum of immunized animals acquires also a specific agglutinative power toward the red cells of the animals in whose blood the immunization was accomplished. The addition of the serum to such blood causes a rapid falling out of the red corpuscles which clump together at the bottom of a test-tube to a dense mass.

Hemolysis by immunization and hemo-agglutination have now been studied with the same uniform results in a great many species of animals, of which the blood of chickens and pigeons (von Dungern),[15] of geese (Metschnikoff),[16] and of frogs (Krompecher)[17] deserve special mention. With the nucleated red cells of the blood of these animals a quantitative study of the hemolytic effect is possible not only in the test-tube, but also in the hanging-drop under the microscope. The number of free nuclei indicate the degree of hemolysis. Furthermore, with these characteristic corpuscles, also the specific character of hemolysis and agglutination is conveniently demonstrable in the hanging-drop. When, for instance, chicken blood and the blood of a mammal—say a guinea-pig—are thoroughly mixed, and to a drop of this under the microscope a droplet of the serum of a rabbit immunized by chicken blood is added, it can then be observed that during the period of agglutination the nucleated red cells of the chicken gather into small heaps, while the red cells of the guinea-pig remain evenly distributed throughout the entire field; in a later stage, when the hemolysis takes effect, the red cells of the guinea-pig remain unchanged, while nothing but nuclei can be seen of the chicken cells.

Immunization is accomplished by the usual methods—*i. e.*; by subcutaneous, intraperitoneal, or intravenous injections. In a very recent communication, however, Metalnikoff[18] reports that he attained immunization also by feeding one animal with the blood of another animal. In a previous communication by Uhlenhuth[19] on antiproteid

immunization, of which we shall speak presently, the possibility of an intrastomachal immunization is already mentioned.

OTHER IMMUNIZATION REACTIONS. Before continuing further our report on hemolysis, we shall stop to call your attention briefly to a number of other remarkable results which the very recent studies in hemolysis and immunity have brought to light. In the first place the conception of immunization against foreign cells—which was derived, as stated above, from the possibility of immunization against red cells as well as against bacteria—was soon extended with success to other body cells. Von Dungern[20] has immunized animals against ciliated epithelia. When these epithelia are introduced into the peritoneal cavity of a normal animal the cilia continue their movements for quite a long time. If, however, the animal has been treated beforehand with injections of an emulsion of such epithelia, the cilia stop their movements very soon after the introduction in the abdominal cavity, and the entire cell becomes rapidly degenerated. The same differences can be observed in the sera of animals within test-tubes.

In connection with these results the idea found expression that it might be possible to obtain a serum protective against malignant epithelial growths. Metschnikoff[21] has immunized animals against leucocytes; these cells become rapidly dissolved in the peritoneal cavity or in the serum of animals which had been previously treated by injections of the emulsion of the spleen or lymph glands. Metschnikoff,[22] Landsteiner,[23] and Moxter[24] have immunized sheep against spermatozoa; these cells lose their motility very rapidly in the peritoneal cavity of animals which have previously received injections of the same kind of cells. All these immunizations are distinctly specific. If, for instance, the animal has received injections of sheep's spermatozoa its peritoneal cavity will exert no influence upon the spermatozoa of the horse, etc. Spermatozoa of immunized animals show also the phenomenon of specific agglutination.

Furthermore, the hemolytic studies brought out facts which stimulated researches regarding immunization against animal substances of a non-cellular character, and these have had extremely interesting results. Tchistovitz,[25] Bordet,[26] and Nolf[27] found that the specific immune sera which affect the red cells by agglutination and dissolution, cause also a distinct precipitate in the blood-serum of the species by whose blood or serum the immunization was accomplished.

Bordet[28] found, further, after the injection of milk into an animal the serum of this animal, when added to milk, causes a precipitation of the proteids of the milk. And Wassermann[29] has shown that this reaction is a specific one. For instance, when the injections are made with cow's milk the serum will cause a precipitate in cow's milk only, and not in the milk of any other animal.

Walter Myers[30] and Uhlenhuth[31] found, after the injection into animals of certain proteids, the sera of these animals produce a precipitate in the proteids employed in the injections; and this reaction, too, is distinctly specific. For instance, when a rabbit is immunized by the whites of hen's eggs the serum of this animal gives no precipitate with any other kind of a proteid except with the egg albumen of a hen's egg.

Practical Application. The specific precipitation of the immunized blood-serum found recently a very interesting practical application: Uhlenhuth[32] Wassermann and Schütze[33] have evolved from it a very delicate method for distinguishing with absolute certainty human blood from that of other animals—*except that of monkeys!* After injection of human blood into rabbits the serum of the latter causes a characteristic turbidity and flocculent deposit in the human blood, even if this is in the form of an old, small, dry spot. The reaction is present even when the human blood is diluted 1 : 50,000 (Stern[34]). The forensic importance of this method is apparent. Further studies have shown that the immunization in question can be accomplished not only by human blood, but also by peritoneal exudates;[35] and what is even more striking, even by albuminous human urine.[36] Serum made to be immune by any of these methods gives a precipitate not only in the human blood but also in dilute albuminous human urine. The outlook for further progress in this direction is very bright.

Mechanism of Hemolysis by Immunization. Turning again to hemolysis by immunization, I have to record the great progress made in the understanding of the mechanism of this process, and here, again, we have to recur to bacteriolysis. In the bacteriology of only a few years ago we often met the term "Pfeiffer's phenomenon." It meant the observation of Pfeiffer that immune sera dissolve bacteria only within the peritoneal cavity, not outside of the animal's body. Metschnikoff,[37] however, has shown that the bacteriolytic process can be ob-

served also in the test-tube if peritoneal exudate is added to the immune serum; and Bordet[38] has shown, further, that even the immune serum alone will dissolve bacteria outside of the body, if it be very fresh. The immune serum loses something by standing, but this can be regenerated by the addition of serum from a normal animal. Immune serum which has been made inactive by heating at 55° C. for half an hour can also be made active again by the addition of such normal serum. Reviewing all these facts, Pfeiffer[39] has formulated a theory which has met with nearly universal approval. According to this theory, fresh immune serum consists of two parts: one component is not easily destroyed by heat, it is thermo-stable, the other one is destroyed by such a low temperature as 55° C., it is thermo-labile. The latter substance is a ferment-like body and is present in the normal sera of animals. The thermo-stable part, which is the new, immunized part of the immune serum, and therefore is the real immune body, is in itself harmless to the bacteria, but it forms the means of bringing the normal proteolytic ferment present in the normal serum to act upon the bacteria to dissolve them. The fresh immune serum contains both; the ferment-like body, however, is very sensitive to all abnormal influences, perishes soon, and is readily destroyed by a temperature of 55° C. When this occurs the immune serum is then inactive, and contains only the inactive immune body; but by the addition of fresh normal serum new ferment bodies are added, and the immune serum becomes regenerated, or "re-activated," to use the technical term.

When Bordet[40] had discovered the hemolysis by immunization he subjected it to the same tests employed in bacteriolysis, and found that heating the serum to 55° C. deprived it of its hemolytic power, and that the addition of normal serum restored this again; thus the inactive serum is regenerated. Bordet, therefore, assumes that the hemolytic immune sera, like the bacteriolytic sera, also consist of two parts—a new, thermo-stable, harmless immune body, and a thermo-labile, sensitive, enzyme-like body, which latter is present also in the serum of normal animals.

We may mention briefly that the hemo-agglutinating and the precipitating properties of the immune serum show a resisting power equal to that of the immune body. A temperature of 60° C. for one hour does not affect them.

EHRLICH AND MORGENROTH'S STUDIES OF HEMOLYSIS. In a long series of ingenious experiments the mechanism of hemolysis has been subjected to a profound analysis by Ehrlich and Morgenroth,[41] who brought to light a number of important facts and general principles, and whose views are now accepted by a majority of the investigators in this new field. The terminology of these writers is new and somewhat complicated, and has its origin in Ehrlich's so-called "lateral-chain theory of immunity." As Ehrlich's theory has been very fruitful in the discovery of many new facts, and is now accepted as the best working hypothesis by a great number of bacteriologists, it will not be out of place to give here a brief sketch of it.

EHRLICH'S LATERAL-CHAIN THEORY. Ehrlich's color-analytic studies led him to the conception[42] that the living protoplasm has, beside its essential part, a great number of lateral mechanisms. The essential part (Leistungskern) is that which distinguishes one cell from another—for instance, a nerve-cell from a blood-cell—while the object of the lateral mechanisms, which Ehrlich termed lateral or side chains (Seitenketten), is to catch external substances and chain them to the main body of the cell. Thus the process of assimilation, Ehrlich thinks, is carried on by means of these mechanisms; the highly complex, large food molecules are trapped by these catchers, split by means of some ferment, and made ready for the use of the cell-body. These mechanisms Ehrlich designates now as *receptors*. According to him, each receptor is adjusted for only one kind of substance, is specific, receptor and substance being fitted for one another like key and lock. By means of these receptors not only food but many other things can be grasped and firmly fastened to the cells—for instance, ferments and toxins, provided these cells have the receptors especially adapted to these toxins or ferments. Animals whose nerve-cells, for instance, have no receptors for the tetanus toxin are immune to tetanus. At present Ehrlich distinguishes three orders of receptors:

First order: single, uncomplicated receptors. They receive, among others, toxins and ferments.

Second order: single receptors, complicated by ferments. These receptors serve, as mentioned above, the process of assimilation.

Third order: double receptors. These Ehrlich now terms *amboceptors*. We shall encounter these terms later in discussing hemolysis.

When the receptors have trapped and fastened corresponding substances they, too, become fixed and, therefore, are lost to the cell-body; the loss, however, is soon made up by the cell regenerating new receptors. Now, Ehrlich assumes that when by frequent introduction of substances the loss and regeneration of the receptors becomes a repeated occurrence, the cell-body, if not succumbing to the overtaxation, is stimulated to overproduction of the receptors—compensatory hypertrophy (Weigert), which then, Ehrlich further assumes, are thrown off into the surrounding fluid, and are finally brought into the blood-stream. Hence, immunization—*i. e.*, frequent introduction of a specific substance—leads finally to an overflooding of the blood-stream with corresponding specific free receptors. If now the specific substance—say tetanus toxin—is introduced into the blood it is caught and fixed by the free swimming receptors within the blood and is thus prevented from getting within the reach of the nerve-cells and their receptors, hence the success of active immunization. Furthermore, if such blood containing free swimming specific tetanus receptors is injected into another animal, it will protect this animal also against the effects of the toxin, because the free receptors within the blood of the new host will catch and fix the invading toxins and thus prevent them from doing further damage. Antitoxin, according to Ehrlich's theory, is the specific receptor torn away from the cell-body and swimming within the blood, ready to catch its special associate, the specific toxin.

Moreover, according to Ehrlich, not only the cells but also all other units of living protoplasm consist of two parts—an essential part and a part whose task it is to form specific unions with other substances or cells. For instance, ferments and toxins consist of a *toxiphoric* or *toxizymotic* group, through which each toxin or ferment differs from every other and exerts its specific activity, and a *haptophoric* group, through which the ferments or toxins become fixed to the receptors still attached to the cells or detached from them.

From the foregoing statement it may be seen that according to the kind of immunization the blood contains detached receptors of the first or second order—*i. e.*, single receptors, uniceptors, or receptors of the third order, amboceptors—*i. e.*, bodies which, like double clamps, contain two receptors. With this latter kind of receptors,

according to the views of Ehrlich and Morgenroth, we have to deal in hemolysis, to which we now return.

The thermo-sensitive component of the hemolytic body (hemotoxin) was at first termed by Ehrlich and Morgenroth "addiment;" they now call it "complement." The thermo-stable part they previously termed "immune body," in hemolysis by immunization, and "intermediary body" in normal hemolysis; now they term it, as stated above, "amboceptor" in both cases. The latter term has not yet been employed by any other writer. The terms "immune body" and "complement" have the advantage over other designations, inasmuch as they express the facts irrespective of any theoretic interpretations.

For the proper study of the exact relations of the complement and immune body to one another and to the red blood-corpuscles, it was indispensable to obtain each component separately. This is an easy task as far as the immune body is concerned. The heating of the serum to 55° C. destroys the complement in most cases, thus leaving the immune body in the inactive serum in practically a pure state. It was quite a difficult task, however, to obtain the specific complement free from the immune body and other complements always present in any serum. The study of the ingenious methods invented by Ehrlich and Morgenroth to throw light into the intricate problems is quite interesting and instructive. I shall, however, restrict myself here to the relation of only one of the fundamental experiments.

A certain number of the red blood-corpuscles which were used for immunization were added to the immune serum and immediately put on ice, where the mixture remained for some time; then, by means of the centrifuge the blood-cells were separated from the serum and mixed with a proper quantity of physiologic salt solution. In this state no solution of the red cells took place. Neither had the addition of inactive (heated) serum (immune body) any effect; but the addition of normal serum (complement) led immediately to hemolysis. Then, again, the addition of fresh red blood-cells to the decanted immune serum cells caused no solution of the blood-corpuscles; such a solution, however, soon took place on further addition of inactive serum. The different phases of this experiment show clearly that during the stay on ice the red blood-corpuscles took up from the immune serum all the immune bodies and none of the complement which remained in a pure state in the centrifugated immune serum.

From this and many other experiments, the details of which cannot be given here, Ehrlich and Morgenroth conclude that immune body and complement exist in a separate state within the immune serum. The red blood-corpuscles, when brought in contact with the immune serum, take up a certain amount of the immune body and form a firm union with it, but take nothing of the complement. The latter, however, is taken up by another receptor of the immune body, and through this connecting link the zymotoxic complement exerts its dissolving influence upon the red cells. Accordingly, the immune body is provided with two receptors, a sort of a double clamp; it grasps with one of the receptors the red cell, and with the other binds the complement. The immune body, however, has a greater affinity—at least within the artificial immune serum—for the red blood-corpuscles than for the complement. The junction between immune body and red cell can be accomplished in a shorter time and at a lower temperature than that required for a successful union of immune body and complement. According to Ehrlich's theory the immune body is a receptor of the third order, which, by the act of immunization, has been thrown off from the red cells into the blood-stream of the immunized animal.

In connection with the foregoing we should mention that, according to the experiments of Nolf,[43] it is the stroma and not the hemoglobin of the red corpuscles which binds the immune body. Furthermore, according to von Dungern,[44] immunization produces only immune bodies, while the proportion of complements which are normally present in the serum remains unaltered.

By a further analysis Ehrlich and Morgenroth have proved that normal hemolysis is similar in nearly all respects to the hemolysis caused by artificial immunization; the hemolytic body, the normal hemotoxin, consists also of the same two components, and the relations to one another, as well as to the red corpuscles, are the same as described above for the immunization hemotoxin. Normal hemolysis is nothing else than a result of immunization which has taken place at one time or another during the life of the animal. Furthermore, when the normal serum of one animal species dissolves the red blood-corpuscles of two or three or more species of animals this serum has been found to contain just as many separate specific hemotoxins. In normal goat's serum, which possessed the power to agglutinate human blood, as

well as the blood of rabbits and pigeons, Malkoff[45] found that upon the addition of human blood to the serum, which was followed by a rapid agglutination of the red cells, the supernatant serum retained its agglutinating power for the blood-corpuscles of the other two species in question. Again, normal goat's serum dissolves red blood-corpuscles of the rabbit as well as those of the guinea-pig. By adding guinea-pig's blood to inactive serum, and then centrifugating it, Ehrlich and Morgenroth proved that the sedimented blood-cells contain the immune body for the guinea-pig's blood, while the supernatant serum contains the immune body for the rabbit's blood. By filtration of normal goat's serum through a "pukalla filter," Ehrlich and Morgenroth established, further, that the filtrate contains the entire complement of the hemotoxin for the guinea-pig's blood, while nearly nothing of the complement for the rabbit's blood passes through the filter. All of which goes to show that the normal serum of the goat, which dissolves the blood-cells of two species, contains separate immune bodies as well as complements for each species.

Ehrlich and Morgenroth have also studied the effect of injections of blood of one individual into another individual of the same species. They found, in fact, that the serum of the receiving individual exerts a hemolytic effect upon the blood of a limited group of individuals of the same species. The individuals of this group, however, may differ among themselves in their behavior toward the serum of another immunized individual. The hemotoxins affecting the individuals of the same species, Ehrlich and Morgenroth term "isolysins," in contradistinction to the hemotoxins affecting those of another species, which they term "heterolysins." Ehrlich and Morgenroth could not establish the existence of "autolysins"—*i. e.*, the serum of an animal which was treated by injections with its own blood did not acquire a dissolving power over its own red blood-corpuscles.

Finally, it has been established by Ehrlich, Bordet, and many other investigators that by injections of immune sera, or normal sera containing specific hemolysins, specific *antihemolysins* are produced in the serum of the receiving animal, the efficiency of which can be easily demonstrated in a quantitative way in the test-tube. According to Ehrlich the antibodies enter into a combination with the haptophoric group of the complement, thus preventing it from joining the immune body and affecting the red blood-corpuscles. A. Schütze and Paul

Müller,[47] however, report that in their experiments the antibodies were attached to the immune bodies.

There are some differences between the views of Ehrlich and Bordet which deserve to be pointed out briefly. The ferment-like component of the hemotoxin (Ehrlich's complement) is termed by Bordet and Buchner[48] "alexin," and both writers assume that it is one and the same proteolytic enzyme which causes all the specific cases of hemolysis as well as bacteriolysis. We have seen above that Ehrlich assumes the existence of a specific complement (alexin) in each and every case of specific hemolysis, and it seems to me that Ehrlich's view is conclusively born out by his experiments.

Another point of difference is the way both authors conceive of the relation between the complement (alexin) and the red blood-corpuscles. Ehrlich's view we have stated above: the complement becomes attached to the immune body, which in turn is attached to the red cell, and hence the name "intermediary body" for the immune body. Bordet assumes that the alexin (complement) directly attacks the red blood-corpuscle, but not until the latter has been prepared in a certain unknown way by the immune body, and hence Bordet's name for the latter—"substance sensibilatrice."

Metschnikoff[49] terms the immune body "fixator" and the complement "citase," which latter term indicates Metschnikoff's theory that the ferment has its origin in the white cells. Paul Müller[50] uses the term "copula" for the immune body.

A few words should be said regarding the term "immunization" employed by all writers for the different specific reactions enumerated in this paper. With the term "immunization" we are wont to combine the conception of the preparation of an entire complex organism to resist the effects of an infection or intoxication. In the present line of studies the term "immunization" is employed to indicate that by the repeated invasion of foreign organic substances a new element, probably of cellular origin, is created in the blood, by means of which the intruder is unfavorably affected. It cannot be denied that in the abstract both definitions have a common ground, since by repeated attacks multicellular or unicellular organisms acquire offensive powers against their assailants. *In praxi*, however, the new application of the term "immunization" is bound to lead to some confusion. Here is an illustration taken from my own experience: in order to immunize a

rabbit against the red cells of the guinea-pig, I injected blood of the latter animal into the ear-vein of a rabbit. The third injection completed the immunization, and the serum of the rabbit dissolved the red cells in a few minutes. This successful immunization, however, sometimes kills the rabbit. The stromata of the dissolved red cells of the guinea-pig form thrombi in the vascular system of the rabbit. Here is a successful immunization which kills the immunized animal. The immunization of a cell is one thing, and the immunization of an animal is quite another thing. It seems, indeed, desirable to have for the unicellular reactions a separate designation, leaving the term "immunization" for the acquisition of defensive powers by the complex organism. However, hemolysis is already crowded with new terms, and I do not feel impelled to the invention of another.

My Own Experiments.

I am coming now to my own experiments. As stated in the introduction, my original undertaking was the state of the changes which alien blood might undergo by a temporary stay in the peritoneal cavity of the receiving species. In the present line of investigation the question was more precise: Do the hemolytic and agglutinating properties of alien serum suffer any changes by such a stay? This question can be studied in the test-tube with reasonable expectation of obtaining precise, quantitative results. But for that purpose I had to employ serum instead of blood, and this serum had to have hemolytic and agglutinating properties, which not all sera possess. In my previous experiments I tested the effect of bull's blood upon rabbits. The preliminary work in my present experiment was, therefore, to establish the effects of bull's serum upon the red blood-corpuscles of the rabbit. As far as I can see, there are no statements regarding this point in the recent literature on hemolysis. It will be, therefore, not out of place to give here a brief account of the results of my preliminary experiments.

Agglutinating Power of Normal Bull's Serum. Regarding agglutination, the statement can be very brief. In the numerous tests I have made I have never observed that normal bull's serum exerts any agglutinating influence upon the red blood-corpuscles of the rabbit.

HEMOLYTIC POWER OF NORMAL BULL'S SERUM. It is different, however, with hemolysis. Bull's serum dissolves the rabbit's red cells. Before going into particulars I have to say a few words regarding the method I have employed. Fresh defibrinated rabbit's blood was employed, and always diluted 1 : 10 of 0.85 per cent. salt solution. Two c.c. of this diluted blood was put into a narrow test-tube and a variable quantity of fresh bull's serum was added. The test-tubes were then kept either in the thermostat at 37° C. or at room-temperature, and then the degree of the eventual solution and the time of its appearance were noted.

As stated above, the red blood-cells of the rabbit are promptly dissolved by bull's serum. The degree of the hemolytic effect varies with each individual from which the serum has been obtained—a condition which bull's serum shares with many other normal hemolytic sera. The variation, however, in our case was confined to narrow limits. 0.5 c.c. of the weakest bull's serum dissolved 2 c.c. of rabbit's blood (1 : 10) in one hour at room-temperature, while there were bull's sera 0.2 c.c. of which dissolved in the same quantity of rabbit's blood within ten minutes, also at room-temperature. Higher temperatures, of course, hastened the solution in every case. By the term "solution" I mean that the blood became laky, perfectly translucent, with no sediment; the stromata, however, could be seen as a fine, flocculent suspension; shaking the test-tube could not alter the condition.

Heating the serum to 55° C. had hardly any influence. To deprive the serum of its hemolytic power, it was necessary to keep it at 57° to 58° C. for at least fifty minutes.

The serum lost its hemolytic power when kept at room-temperature for ten to fourteen days. At a low temperature the hemolytic power was preserved much longer.

The hemolytic property of bull's serum differs from that of many other hemolytic sera with regard to regeneration; of this, however, we shall have to speak later.

INFLUENCE OF A SOJOURN OF BULL'S SERUM IN THE PERITONEAL CAVITY. After this preliminary statement I can now turn to the problem in hand. The chief result can be briefly stated: *When normal fresh bull's serum is brought into the peritoneal cavity of a rabbit and left there for three hours the recovered serum is found to have lost all or most of its hemolytic power.* The loss is less when

the sojourn is shorter. It is impossible to keep the serum in the abdominal cavity much longer than three hours, for the animal usually dies after three and one-half hours.

In most of the experiments a part of the serum was absorbed during its sojourn in the peritoneal cavity. I saw, however, two animals from which I recovered after three hours more fluid than I had introduced. In neither of these cases was there any difference regarding the loss of the hemolytic power. In two experiments in which I found the hemolytic power only considerably reduced I introduced the recovered serum into the peritoneal cavity of another rabbit, and removed it again after fifteen minutes; the serum was now found to possess no hemolytic power whatsoever. On the strength of these observations we can base the following statements: The normal hemolytic power of bull's serum for red blood-corpuscles of the rabbit disappears during a stay in the peritoneal cavity of this animal; the disappearance is the greater the longer the sojourn, and is independent of the absorption of the fluid; disappearance takes place even during the first fifteen minutes.

I will describe a few notes for illustration:

1a.	2 c.c. rabbit's bl.	+ 0.5 c c. nor. bull's ser.	= after 50 min. Clear solution	19° C.
1b.	2 c.c. "	+ 0.5 c.c. per. "	= slightly dissolved above dark sediment after 17 hours	19° C.
2a.	2 c.c. "	+ 0.5 c.c. nor. "	= in a few minutes perfectly laky	in thermostat 37° C.
2b.	2 c.c. "	+ 0.5 c.c. per. "	= after 24 hours undissolved	in thermostat 37° C.
3a.	2 c.c. "	+ 0 5 c.c. nor. "	= after 10 minutes dissolved	21° C.
3b.	2 c.c. "	+ 0.5 c.c. per. "	= after 70 minutes very slight solution after nine hours quite laky, black deposit	21° C.
3c.	2 c.c. "	+ 0.5 c.c. per. per.* bull's ser.	= after 9 hours no change whatsover	21° C.

ABSENCE OF HEMOLYSIS NOT DUE TO ANTIHEMOLYSIN. What is the nature of this change in the hemolytic power which takes place in the peritoneal cavity? The disappearance of the hemolytic power may be due either to the subtraction of one of the components of hemolysis or to the addition of antihemolysin. I shall discuss the last proposition first. I tested it by determining the minimum quantity of normal bull's serum which still dissolves fairly distinct in a reasonable time, and

* Per. per. means that the peritoneal serum was transferred into the peritoneal cavity of another rabbit for fifteen minutes.

then adding to it peritoneal bull's serum. The outcome was negative. Even the addition of 1 c.c. of the peritoneal bull's serum had no visible influence upon the hemolytic effect of the predetermined minimum of the normal bull's serum. I have also washed out the normal peritoneal cavity with physiologic salt solution and tested the fluid for antihemolysin, with a negative result.

Disappearance of Hemolytic Power in the Peritoneal Cavity of a Dead Animal. Moreover, the following interesting fact speaks also against the assumption that the loss of hemolytic power within the abdominal cavity is due to an addition of some factor. I have repeatedly established that the hemolytic effect disappears also when the bull's serum is kept for a few hours in the peritoneal cavity of a dead rabbit. The loss is somewhat smaller than that which takes place in the living animal. Now, it is not very probable that a secretion of an antihemolysin takes place in the peritoneal cavity of a dead animal! That absorption of fluid from the peritoneal cavity takes place also in a dead animal we know from the experiments of Hamburger[51] and of Adler and myself.[52] With the definition of absorption, as it was given by Adler and myself, the process is easily understood. We divide absorption into two phases: The first phase is the entrance of fluid from the peritoneal cavity into the interstitial spaces; the second phase is the entrance of the fluid from the interstitial spaces into the blood-stream. The latter phase does not occur in the dead animal, as there is no blood-stream. The first phase is affected chiefly by imbibition, a process which takes place also in dead tissue. Therefore, the entrance of the whole fluid, or part of it, from the peritoneal cavity into the surrounding interstitial tissue can and does take place also in dead animals.

The disappearance of hemolytic power of the serum from the peritoneal cavity is apparently due to a subtraction, to an absorption of one of the components of hemolysis. But which of the components is it, the immune body or the complement? Regarding the immune body the determination was easy. Bull's serum heated at 57° C. for one hour, as a result of which it becomes inactive (immune body), was added to the inactive peritoneal serum, and both were added in sufficient quantities to rabbit's blood. It had no influence. It is, therefore, not the immune body which becomes absorbed in the peritoneal cavity.

It would thus appear that it could be only the complement which became absorbed. However, the test was disappointing. Following the lead of Bordet, Ehrlich, etc., I have tried to regenerate the inactive peritoneal serum by the addition of normal serum. I have tried fresh normal serum of the rabbit, guinea-pig, and sheep. I have tried horse serum,* which is said to be rich in various complements—but all failed. I followed out the suggestion of Delezenne[53] and obtained by centrifugation of rabbit's blood fresh serum ready for use half an hour after the blood was drawn, but all in vain. So far I have not succeeded by the addition of any normal serum in regenerating the peritoneal serum.

INACTIVE BULL'S SERUM CANNOT BE REGENERATED. However, the failure to regenerate by normal serum does not necessarily indicate that it is not the loss of the complement which made the peritoneal serum inactive. According to universal experience the inactivity of the heated serum is surely due to the destruction of the complement. Nevertheless, I did not succeed in regenerating heated bull's serum by any normal serum. Neither could I regenerate bull's serum which had become inactive by standing fourteen days at room-temperature.

It is a singular and interesting fact, that the hemolytic force of normal bull's serum when once made inactive cannot be regenerated, at least not by the usual methods. The only other similar exception I know of is that of eel's serum, of which Ehrlich and Morgenroth[54] report that if it is once made inactive (by heating it fifteen minutes at 54° C.) it cannot be made effective again.

EFFECT OF THE PERITONEAL CAVITY UPON IMMUNE SERUM. The next step in the line of my investigation was the inquiry whether immune serum also becomes inactive by a temporary stay in the peritoneal cavity. I selected for my study the serum of rabbits immunized by guinea-pig's blood. To save material and time I immunized the rabbits by injecting guinea-pig's blood into the circulation through the ear-veins. I shall record here a few observations which I have not seen reported elsewhere. I used for each injection only 1.5 c.c. of the blood, repeating them at intervals of five to six days. I could never make more than three injections—a fourth injection was sure

* I wish to thank Dr. William H. Park, who kindly provided me with horse serum.

to kill the animals; they usually died under convulsions within four to five minutes after the injection. They die sometimes even soon after the third injection, and, therefore, one must, when the third immunizing injection is made, be ready to obtain the blood if one is not to lose the experiment. Intravenous injection of blood into an animal against which it is already immunized kills the animal, probably through the formation of thrombi in vital points, either by the agglutinated foreign blood-cells or by the masses of the stromata from the dissolved red cells.

Before making the second or third injection I often obtained some blood from the ear-vein of the rabbit and tested the effect of the serum upon the blood-cells of the guinea-pig. I thus observed that agglutination of the red blood-corpuscles was the first effect which appeared in the serum of the immunized animal. It appeared sometimes even after the first injection, while there was as yet no sign of hemolysis. After more injections, when the hemolytic effect became intense and rapid, the process of agglutination could hardly be observed. In some cases, moreover, both phenomena were distinctly present.

In these cases the agglutinating effect starts immediately on the addition of the serum to the blood, and soon dense red masses are seen to accumulate at the bottom of the test-tube, in which the hemolytic process progresses quite slowly. Heating the serum for thirty minutes at 55° C. destroys hemolysis, but not agglutination. By this means the process of agglutination can be made visible even in cases in which the process of agglutination could hardly be observed.

We come now again to our leading experiment. Serum of an immunized rabbit was introduced into the peritoneal cavity of a normal rabbit, left there for three hours and then recovered. Such peritoneal serum, when added to guinea-pig's blood, agglutinated it, but caused no hemolysis whatsoever. Addition of immunized rabbit's serum, made inactive by heating, to peritoneal serum had no regenerating effect. But the addition of fresh normal rabbit's serum to the immunized peritoneal serum regenerated it completely; the mixture of both sera dissolved guinea-pig's blood as readily as the active immunized serum alone. The following notes of the experiments are illustrative:

4a.	2 c.c.	g.-p. bl."	+ 0.5;	"C. im. ser."	= dissolved in a few minutes.
4b.	2 "	"	+ 0.5	"per. im. ser."	= after eight hours undissolved.
4c.	2 "	"	+ 0.5	"im. ser. 55"	= after eight hours undissolved.
4d.	2 "	"	+ 0.5	"per. im. ser."	+ 1.0 "fr. rab. ser." = dissolved in a few minutes.
4e.	2 "	"	+ 0.5	"im. ser. 55"	+ 1.0 "fr. rab. ser." = dissolved in a few minutes.*

There was prompt agglutination in every one of the five tests.

These experiments teach us that immunized serum also, when kept for a few hours in the peritoneal cavity, becomes inactive. But here we have seen that on the addition of fresh serum of a normal rabbit it becomes active again, and this furnishes us with the looked-for proof that the loss of the hemolytic power in the peritoneal cavity is due to the disappearance of the complement from the remaining fluid in the peritoneal cavity. Agglutination does not seem to become visibly affected by a stay in the peritoneal cavity.

CHIEF CONCLUSIONS. Normal and immunized sera lose their hemolytic power during a prolonged stay in the peritoneal cavity. The loss is due to the disappearance of the toxic component, the complement of Ehrlich, or the alexin of Bordet and Buchner. The disappearance means absorption, and the disappearance of the complement in a much greater proportion than the balance of the fluid means elective absorption. However, as this elective absorption takes place also in a dead animal, it cannot be a vital phenomenon; it is rather probable that it has its explanation in some laws of osmosis and imbibition.

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* "g.-p. bl." = guinea-pig's blood, 1:10; "C. im. ser." = serum from immunized rabbit C.; "per. C. im. ser." = peritoneal serum from immunized rabbit C.; "C. im. ser. 55" = serum from immunized rabbit C. heated at 55° C.; "fr. rab. ser." = fresh serum from normal rabbit.

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A BRIEF REPORT OF THE CLINICAL, PHYSIOLOGIC, AND CHEMICAL STUDY OF THREE CASES OF FAMILY PERIODIC PARALYSIS.

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In 1899 one of us (Mitchell) reported to this Association a study of a case of family periodic paralysis. The present is a brief statement of two other unpublished cases of the same disease and the results of minute study of the blood, urinary, and gastric conditions in them, and also in the individual furnishing the material for the paper presented in 1899:

Case I.—Mrs. A., born in the United States, aged thirty-five years, is an only child. Her father had the same periodic attacks from childhood, but grew better as he grew older. He died of phthisis at forty years of age. A paternal uncle was also subject to them; the first attack of the two brothers occurred in childhood and on the same day. No other cases have been known in the family except those hereafter to be described. Mrs. A. had her first seizure at four years of age, but few afterward until her thirteenth year, since which time they have been of frequent but irregular occurrence. Her general health is poor, and she bears evidence of a healed tubercular process at the right apex. She never has ordinary indigestion, although she suffers from the paralytic seizures if she eats too largely or of too rich or sweet food, especially the last.

Examination. A slight, thin woman, somewhat anemic in appearance; weight, 92 pounds. Except for an impaired resonance at the apex of the right lung, with high-pitched inspiration and prolonged expiration, there is no abnormality noticeable in the physical examination.

The knee-jerks are small, capricious, readily reinforcible; arm-jerks and elbow-jerks normal; pupillary reflexes normal; other reflexes unaltered. Station good, general sensibility wholly unimpaired. The patient's rather anemic appearance was borne out by the blood-count.

When seen in an attack the symptoms were those of a typical case of periodic paralysis of a not very severe sort. The beginning is usually in the

evening; sometimes soon after the evening meal, sometimes later, she begins to have a sense of stiffness with weakness in the legs, which gradually increases until she walks or rises from a chair with great difficulty. The anterior thigh muscles are most and earliest affected, so that in an attack, even of slight degree, she cannot go up stairs at all. There is no warning of the onset, no pain or soreness, no objective rigidity; often she is unaware of the beginning of a seizure until she attempts a movement. The extent of impairment varies from slight weakness to almost total paralysis. Usually the arms are but little affected, but in the severer attacks they suffer nearly as much as the legs, but they are never attacked separately from the legs. Sometimes she wakes in the night to find herself completely paralyzed. The sphincters are not involved.

The decline, like the onset, is gradual. She seldom has more than one attack in twenty-four hours. If the seizure is severe she is quite certain to be free from any trouble for the day following it.

The attacks can be readily induced by eating sweets, notably chocolate. They are worse if she permits herself to become very constipated. They are increased in severity, if not brought on, by nervous or mental fatigue and worry, but she states distinctly that they are not made worse by bodily exercise, even to the point of fatigue. Indeed, both she and her daughter assert that if they perceive a seizure approaching they can "walk it off." A number of spells were observed while she was under treatment, differing only in the extent and degree of the paralysis, which was sometimes total below the waist at the height of the attack, sometimes involving the arms in a less degree, sometimes not weakening them at all, and sometimes affecting them equally with the legs. The appearance of the patient is very little changed during an attack, unless it be a very marked one; in that case she looks paler than usual, her circulation is somewhat below its normal force, her tongue coated. There is no heart murmur, such as is present in Case III. The power to swallow is unaltered, but she cannot take a full breath or cough voluntarily.

The knee-jerk and the various superficial and deep reflexes peculiar to the areas affected disappear altogether during the attacks. Direct muscle stimulation does not cause contraction. Electric contractility is abolished in the severe attacks, or at least is so reduced that nothing short of a violently painful current will produce muscular reaction; when any effect can be had CA Cl C is always greater than AN Cl C. In the slighter seizures there is only some impairment of contractility.

Case II.—Miss A. A., daughter of the above patient, aged thirteen years, also an only child, is the fourth instance of the palsy in this family. She is a well-made, ruddy girl, much more strongly built than her mother. At six years of age she suffered her first seizure of the family disorder, supposed to be brought on by improper food and overexertion. She remained free afterward for about three years, when she had another "fit," and soon after began to have them every three months, always at night, like her mother. In

August, 1900, her first menses appeared, after which she had attacks frequently for three weeks. When first seen (October 20, 1900) she was having about two a week. The onset and decline are both gradual, as in the mother. She has never been completely paralyzed, the enfeeblement being usually limited to the legs, and amounting to great weakness and a sense of stiffening. The arms have rarely been involved at all, and never unless the legs were affected, and the whole attack is much less severe than in Case I. Sensation is not altered during the attacks. There is no heart murmur. The mental functions are in no way disturbed in either patient. The mother is worse just previous to her menstruation; the girl has her worse attacks during that period.

The electric statement made for the mother will answer for the daughter —namely, that there is an impairment of all forms of contractility during the paralysis.

The girl is not anemic. The urine in both patients during an attack is scanty, loaded with urates and uric acid, and of extremely high acidity, but otherwise normal to ordinary examination. On one occasion a faint trace of albumin was found in the girl's urine during an interval.

CASE III.—C. J., now twenty-one years of age, was fully reported two years ago. His first attack occurred in his thirteenth year, and he is the fifth person in three generations of his family known to have suffered with these seizures—viz.: his mother, his maternal grandfather, a maternal uncle, and a maternal first cousin (a girl of fifteen years). The attacks have happened since their original onset in steadily increasing numbers. When he was seen in October, 1898, they had returned with remarkable regularity about once a week for some weeks. They were somewhat irregular while under treatment in the Infirmary for Nervous Diseases, but since he left the hospital in the spring of 1899 they have re-established about the same periodicity.

If there is any difference between the attacks at the present moment and those occurring three years ago, they are now somewhat more severe and more prolonged than they were then. They still usually begin at night, perhaps with some precedent warning in the shape of a slight weakness of the legs in the afternoon or evening. The only difference in the symptoms is that the heart murmur, at that time heard only in the attacks, is now constant. This is a systolic murmur limited to the pulmonary area and transmitted somewhat up and down the left side of the sternum, and a split second sound heard best at the second interspace, lessening in intensity toward the apex. No alteration in the outline of the heart is demonstrable at any time.

His general appearance during an attack is peculiar. He becomes pale, even his lips losing color; his tongue is coated, his breath heavy smelling and unpleasant; he has no desire to take food, and experiences some difficulty in swallowing. There is a question of whether the involuntary muscles as well as the voluntary are affected, as he cannot take a long breath or cough or sneeze, and has trouble in voiding urine, though these difficulties may be

wholly due to the palsy of the voluntary muscles. Patellar, abdominal, testicular, and elbow reflexes are abolished, the electric reactions entirely lost to every form of stimulation short of a dangerous and painful current while the paralysis lasts. When he begins to improve the attack passes off very rapidly, so that in half an hour or less he becomes entirely able to get about, his reflexes and muscular reactions are regained, and he feels perfectly well except for slight muscular soreness.

It has been noted this time that the impairment, if not the loss, of the knee-jerk seems to persist for hours after he has begun to improve in other respects, and it sometimes has been difficult to elicit even when he was able to be up and walk about the ward. The young man himself describes the attacks as at present more complete and lasting somewhat longer than has previously been the case, the duration, formerly twenty-four to thirty-six hours, being now usually forty-eight, and occasionally even longer.

Mrs. A., an intelligent, well-educated woman, had made for herself the interesting observation that potassium citrate in good-sized doses would cut short an attack. This together with the extremely acid urines of Cases I. and II. suggested a study of the alkalinity of the blood and urine, and at first we thought we had secured interesting results, which have, however, not been confirmed by subsequent study. We will describe these results in more detail later.

We examined also the effects upon rabbits of injection of blood-serum from Case I. Our intention was to inject serum taken during a paralytic period and endeavor to discover if any effect were produced by it upon the knee-jerk in rabbits.

Forty c.c. of blood was drawn from the median basilic vein of Mrs. A. by a sterile syringe and placed on ice in sterile vials. Forty-eight hours later it was centrifugalized to separate the serum completely.

After some work to determine a sort of normal curve of knee-jerk in the rabbit, 4 c.c. of the serum was given into an ear-vein of a rabbit and a series of tracings made of the knee-jerk, as elicited at intervals, for forty-eight minutes after. No effect upon the knee-jerk could be observed.

A second injection of 3 c.c. was given to the same rabbit a little over an hour after the first. Tracings made five, twenty, and twenty-eight minutes after showed no decided change from the normal record. When forty minutes had elapsed the knee-jerk seemed more irritable than normal. Much muscle tremor was noticeable, and somewhat interfered with the clearness of the tracings.

It was curious to note that crossed reflex was very constant in both the rabbits used. The injected rabbit was found dead the next morning. The lethal dose of human serum for the rabbit may be below 1 per cent. of body-weight; a dose of normal serum of the same size would probably have destroyed him in the same time.

A second series of experiments was made ten days later with blood drawn during another and much more severe attack. The patient's blood on both occasions flowed very badly, and it was necessary to introduce the needle a second time into another vein to secure the desired amount.

Injections were made into rabbits in (1) the femoral artery, the vein being ligated. No difference could be noted between tracings made before and after the injection or between reflex upon the injected and that upon the untouched side. (2) Into the anterior thigh muscles; no effect. (3) After trephining an injection was made under the cerebral meninges. No effect upon the knee-jerk could be discovered an hour later. (4) Serum injected into the spinal canal in the lumbar region at two different levels; no effect. (5) Injection into the sheath of the left sciatic nerve. A trifling increase of knee-jerk was observed twenty minutes later, probably due to irritation from the operation of exposing the nerve sheath.

These experiments (given only in outline) were wholly inconclusive, and not in any way satisfactory. We think it possible that rabbits were not the best subjects, and that animals with digestive tracts and food habits more nearly approaching the human type would be more suitable, and perhaps give results of more value.

It is, however, interesting that the few trials undertaken confirm the negative results of the attempts of one of us (Mitchell) to find toxic qualities in the blood or urine of Case III. when previously studied in 1898–99.

Blood examinations were made in Case I. to determine the alkalinity of the blood. Only two determinations could be made—one during the attack and one during the interval. In both of these Löwy's method was used. The woman showed in the interval an alkalinity equivalent to 464 mg. of soda; during the attack the alkalinity was 224 mg. The former figure is distinctly high, but the latter not unusually low, or, at least, not low enough to be considered indicative of an acid intoxication. She had been using alkalies in-

ternally in full doses until forty-eight hours before the first estimation; possibly the high alkalinity was due to this, and the second figure represents more nearly the patient's normal.

In the second patient no examination of the blood was made. In the third the examination in three attacks practically showed no difference in the alkalinity, the figures being respectively 512 in an attack, in the interval 496, and in the next attack 504—all somewhat high figures.

The urine in Cases I. and II. during an attack showed a condition of such marked acidity as to suggest the need of more minute study of the alkalinity of the urine. Accordingly it was carefully investigated for acetone, diacetic acid, and lactic acid. The results were negative in all these examinations.

More important negative results still were obtained from the estimation of the ammonia of the urine in Case III. The figures for twenty-four hours never passed 1½ grams of NH_3 except in one instance, when over three grams were passed, and this latter was a doubtful examination owing to some carelessness in the preservation of the urine on that day. The ammonia (NH_3) was estimated through five attacks and their corresponding intervals. Preceding the first attack in which this was done, the figures for several days were astonishingly low considering his diet. The urine contained only about 100 mg. of ammonia, or even less—a low figure. Since muscle metabolism would seem to be an important source of the acids produced in the body, and is probably, indeed, the chief source, the low ammonia figures suggested that there might be decided qualitative and quantitative alterations in muscle metabolism as well before as during the attack.

Tests of the toxicity of the urinary secretion were made during the height of an attack, and the blood-serum taken during the same attack was tried at the same time. In neither substance could an increase of toxicity be demonstrated, rabbits surviving the injections without any apparent effects.

The examination of the stomach contents of Case I. on two occasions during severe seizures gave one curious result, viz., even starch digestion was not proceeding, and there was a total anacidity, showing the whole digestive process to be absolutely at a standstill, and the gastric motor power diminished or abolished for the time.

The low ammonia content of the urine suggested to Dr. Edsall to

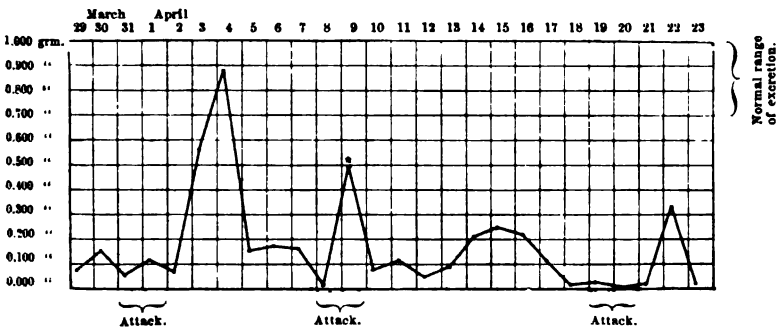
make daily estimations of the kreatinin excretion, hoping thus to discover something of the causation of the disorder. The Neubauer-Salkowski method was used in all the determinations.

Our knowledge of variations in the excretion of this substance is not great. Normally on mixed diet the excretion usually runs between 700 mg. and 1 gm. In muscular dystrophies, extensive paralysis, and other conditions in which the activity of the muscles or their bulk is largely reduced the excretion is much below the normal, while during the process of wasting of muscles, as in cachexias, and also after severe over-exercise, the amount increases. Diet also influences the excretion largely, and, further, very severe anemias are accompanied by an extremely low secretion. With the exception of the conditions of anemias, practically all these points, as well as the fact that kreatinin, or more particularly kreatin, from which kreatinin is derived, is found in large amounts in muscular tissues only, indicate very strongly that these substances are, in chief part at any rate, products of muscles, and possibly are produced practically solely by the muscles. The conditions in severe anemias do not, of course, necessarily contradict this view, as metabolism in general is so largely disturbed in such disorders.

The results of the estimations are shown roughly in the chart. There is in each instance a period of several days of extremely low kreatinin excretion preceding the attack and lasting into the attack or beyond it. Following this there is a sudden rise of the excretion from a point ranging between 3 and 80 mg. up to as high as 880 mg., and then, after reaching this normal or nearly normal level, the excretion falls again and a similar course occurs once more. The abnormal figures are evidently not due to the attack, as they precede it, while those figures approaching the normal occur directly after or with the attack. The very striking relation of the kreatinin excretion to the attacks is evident throughout the series of estimations, and it seems almost unquestionable that, in this case at any rate, the kreatinin is an index at least of alterations in metabolism leading up to a seizure, to be followed by conditions approaching the normal. The cycle then begins again. The relation of the kreatinin to attacks and intervals is most evidently seen in the unusually long period intervening between the second and third attacks. The kreatinin figures rise at the end of the second attack, and then fall at once, but there is another rise which,

though relatively slight, persists for three days, and apparently is the evidence of sufficient improvement in his condition to postpone the onset of the next attack, for this interval was three days longer than the usual one. This correspondence between the rise of kreatinin excretion and the period of freedom from paralysis is curiously striking. A somewhat similar relation may be observed between the relatively low rise in excretion at the period of the third attack and the brevity of the freedom from symptoms following this low excretion. While there was not an actual attack the man had all the usual feelings of an approaching attack on the fifth day after the seizure of April 24th, and was unwilling to go out of the hospital because he feared that he would be overtaken by his paralysis. As just noted, the rise in kreatinin excretion with the end of the preceding attack had been relatively slight and had not persisted.

CHART OF KREATININ EXCRETION—PERIODIC PARALYSIS.



* This figure is certainly too low. Some of the urine (about one-fourth) was sent to Dr. Flexner. The actual figure when reckoned for the whole amount of urine would be 668 mg.

The changes in kreatinin excretion might possibly have been explained on the basis of alterations in the amount or character of the food taken, or have been considered the result of the temporary absolute disuse of the muscles had these changes occurred only immediately *within* the period of the attack, but the striking fact about the kreatinin figures is that they were extremely low for a number of *days before each attack* when the man was taking full diet, and the rise in excretion in the second attack shown on the chart came actually within the period of the attack, and consequently within the time of practically total abstinence from food and total disuse of the muscles.

Further, the relation of intake of nitrogenous foods to the kreatinin excretion was controlled by coincident daily estimations of the total nitrogen of the food (Kjeldahl method), the results with the nitrogen demonstrating absolutely that the total decomposition of nitrogenous food and tissue was at least as high during the periods of low kreatinin excretion before the attack as it was at other times, the only actual falls in excretion of nitrogen coming during the period of the attack, when he was taking very small amounts of food. Another possible source of error that had to be considered was that some of the kreatinin might not have crystallized out as kreatinin zinc chlorid on the days of apparently low excretion and been lost in the filtrate. But that this was not the case was shown by using Weyl's and Jaffe's tests with the alcoholic filtrate. Only faint traces were ever found during these periods, and often none at all; one expects to find traces dissolved in the filtrate under ordinary circumstances.

So far, then, as general conclusions may be reached from the study of one case, it may justly be considered that the attacks are due to metabolic disturbance, and that this disturbance is in all probability situated chiefly or primarily, perhaps entirely, in the muscles themselves. Our knowledge of the excretion of kreatinin in disease is not yet sufficient to state definitely that the disturbance ultimately producing an attack begins in the muscles alone; this seems distinctly probable, however, and at any rate it is practically clear that the present disorder is one of metabolism. A rather striking analogy with gout may, of course, be readily drawn at once, though the variations in the kreatinin excretion in this case are certainly much more striking than any that have been well demonstrated in the uric acid of gout. Whatever be the relation of uric acid to gout, it cannot be reasonably suspected that the disturbance in this case is due to *retention* of kreatinin or kreatin. The figures seem to demonstrate that it is not possible that the variation could be due to retention; they are almost certainly due to a reduction in the formation of these substances, and we believe the kreatinin is only an index of the disturbance of metabolism. There is also no reason to think that such a retention would reduce these symptoms.

Some further study of these questions is, of course, intended, but it has not been possible to complete it before presentation of the present paper and this brief outline of our findings.

It would be interesting to know the effect upon the attacks of moderately severe *over*-exercise a day or two *before* the expected attack. It is possible that this might serve to stimulate metabolism sufficiently to postpone the attack at least, though it might produce just the opposite effect. Some support is given to this theory by the statement of patients, not only ours, but E. W. Taylor's and some of the German cases, that exertion would temporarily postpone an attack, often at the cost of a seizure of greater than the usual severity later. This is not incompatible either with the other observation that exertion in certain instances has *induced* the paralysis.

It is also very important that we should learn the condition of kreatinin excretion in epilepsy, myasthenia gravis, and some other conditions which promise to teach us something concerning its relation to disease.

The practical aspects of the cases as to treatment are interesting and highly unsatisfactory. In Case III. strict diet, baths, and exercise made no change in the periodicity or length of the attacks. Colon lavage and intestinal antiseptics by the mouth were no more successful. Quinin, bromids, and strychnin were administered at different times, and the results again were negative. The slow flow and the dark color of the blood when venesection was performed suggested hypodermoclysis, which was twice tried without good effect. As already noted, Mrs. A., Case I., had observed that potassium citrate had a favorable influence. As a prophylactic, potassium citrate seemed to have some small but uncertain effect in Cases I. and II. in doses of 45 to 60 grains a day. In Case III. it did not reduce the frequency of occurrence. Administered at the beginning of a seizure in repeated large doses (75 to 120 grains) it certainly shortened and mitigated the paralytic period in all three patients. The attacks were so much more regular, both in recurrence and duration, in Case III. that it was easier to judge. His seizures occurred every seventh or eighth day with great punctuality, and lasted almost exactly forty-eight hours, the shortest one which was observed without interference being about twenty hours; but this was the only one out of twelve which extended to less than thirty hours. It is, therefore, fair to infer when four attacks treated with the potash salt only endured twenty-four hours each that this shortening was due to the drug. Another attack during this period treated by hypodermoclysis ran as usual

close to forty-eight hours. It is curious that with Case I., and to a less extent with Case II., a similar though not so marked an influence upon the seizures was shown by potassium bromid, a drug which did not prove of any value in Case III.

In view of the fact that potassium citrate is absorbed as the carbonate, it was thought that a quicker and perhaps stronger effect would be produced by the latter salt. This did not prove true when tried in practice, the attacks being much less influenced by the carbonate than by the citrate. Through a druggist's error on one occasion Case I. took potassium chlorate instead of citrate. The result was not quite so decidedly favorable as when the latter salt was used, but better than when the carbonate was given. Sodium bicarbonate was tried upon several occasions, but seemed to have little effect.

In conclusion, we would reaffirm the statement already made that our endeavor has been to state facts as we have observed them, and not to propound a theory. The time for theorizing must be postponed until further study is possible of this curious condition and some of its possible analogies.

DISCUSSION.

DR. PUTNAM: I have tried potassium citrate on the patient whose case was reported by me last year, but I am sorry to say without success. My patient also had his attacks brought on at times by severe exercise, and occasionally he also could work the attacks off if he could manage to drag himself about.

The ultimate cause of the disease is too subtle to be reached by the chemical analysis of secretions.

DR. MELTZER: The efforts of Dr. Mitchell were, as I understood them, in the direction of finding the cause of this condition. I would like to ask Dr. Mitchell first what is his opinion regarding the nature of this condition. I do not know of any condition in which the muscle would not respond for days to direct faradization. I do not know, either, of any poison that will cause a temporary absence of response to local muscle stimulation. Beside, the explanation of Dr. Mitchell, that the condition might be due to a poison accumulating in the muscles, would require still another explanation as to why certain other muscles, for instance those of the eyes, face, etc., do not participate in this peculiar paralysis. Such a distribution would rather indicate that the location of the cause is not to be looked for within the muscles but rather in the spinal cord.

DR. MITCHELL: We made at various times every possible examination of the muscles, and it is not correct to say that the involuntary muscles did not share in the paralysis. They did take part, as this patient has trouble with his diaphragm and other respiratory muscles; his bowel movements are suspended at the times of the paralysis, and occasionally he cannot even urinate. As to the question of local stimulation of muscles, we found that to produce an electric contraction required more than three times as much as is required to stimulate the normal muscles, even with needle electrodes piercing into the muscle substance. We have no theory to offer in regard to the poison except that suggested here two years ago, that a poison could be imagined which should have a selective action on the muscles and on the cord. Certain poisons are specially prone to affect certain muscles and nerves, as is seen in lead and mercurial intoxications; and if this is not a local muscle poison, what is it? The only thing that is even said to produce effects of this character is curare in large doses—and even this is disputed by the best authorities.

DR. JACOBI: These cases sound to me very much like hysteria. Why not call them hysteric paralysis?

REPORT OF THE PROGRESS OF CASES OF PERNICIOUS ANEMIA PRESENTED TO THE ASSOCIATION IN 1900, AND REPORT OF A CASE OF PERNICIOUS ANEMIA, WITH DIFFUSE SPINAL-CORD LESIONS AND POSTMORTEM FINDINGS.

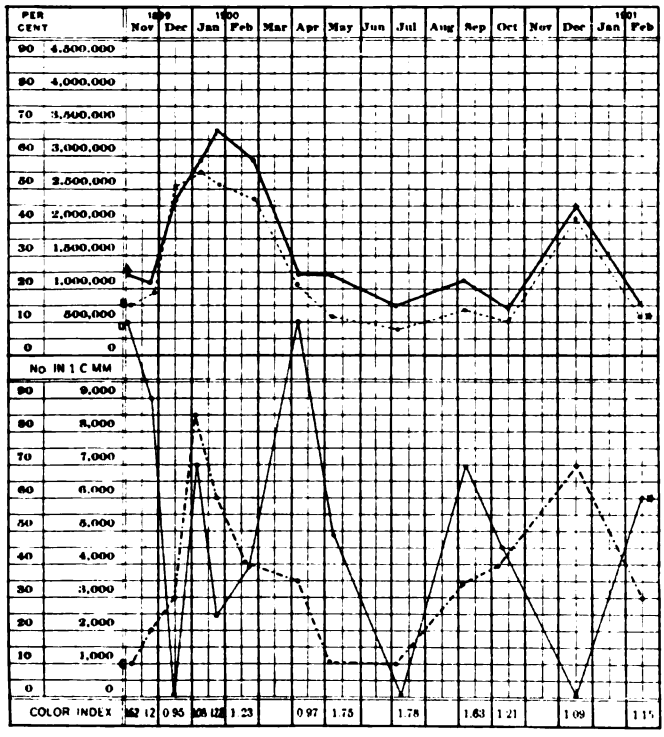
By FRANK BILLINGS, M.D.,
OF CHICAGO.

Of the twenty cases reported last year to the Association ten were dead. During the year, of the remaining ten, four have died; of the remainder, two have disappeared and four are still under observation. No further observations were made of three of the four who died because of the residence in remote localities, and no autopsies were held upon them. The fourth patient (No. 14 in the series) died in February, 1901, and since the first report many examinations of her blood have been made. Last May, when her case was reported, she was on the decline. She remained in this low state until October, when an improvement wave began, which reached its height in December. At that time she had over 2,000,000 red cells and about 40 per cent. of hemoglobin; then a rapid decline occurred, with a fall to less than 20 per cent. of hemoglobin and 659,000 red cells per c.m. The white cell count kept pace with the improvement in the red cells and hemoglobin, and fell with the decline of the other elements of the blood just as was noted in the report of last year. During the decline there was a large increase in the number of nucleated red cells. The accompanying chart shows graphically the blood curve in this case. Unfortunately, no autopsy was allowed. (Chart I.)

Of the patients still living observations have been continued upon Cases Nos. 10, 12, and 13 of the series. When reported last year No. 13 was upon a wave of improvement, and this wave has remained

unbroken up to the present time. The number of red cells, the percentage of hemoglobin, and the number of white cells are about normal. There have been no nucleated cells found since January, 1900. The patient, however, does not look as well as the condition of the blood would indicate. There is a yellow tinge of the skin. He is not strong, and has less endurance than before the illness began.

CHART I.

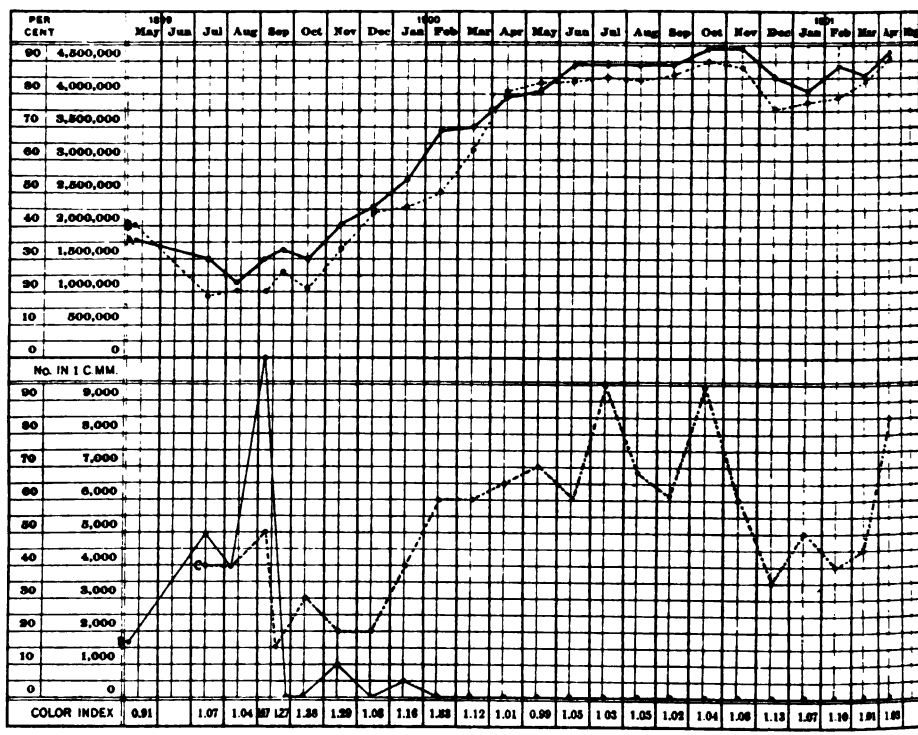


A. Hemoglobin. B. Erythrocytes. C. Leukocytes. D. Nucleated reds. * Death.

Furthermore, the blood cells still show irregularities of form and size. It is not improbable that his improvement wave will be broken by a fall in the near future. The case is a remarkable one because of the long wave of improvement. The chart shows graphically the condition of his blood during the two years he has been under observation, and it is to be noted that even in this stage of improvement the color index has remained high. (Chart II.)

No. 12 returned from Iowa to Chicago in September, 1900, and since that time has been under weekly observation. She has had various waves of slight improvement and decline, with the constant presence of nucleated cells and a high color index. At this date she

CHART II.



A. Hemoglobin. B. Erythrocytes. C. Leukocytes. D. Nucleated reds.

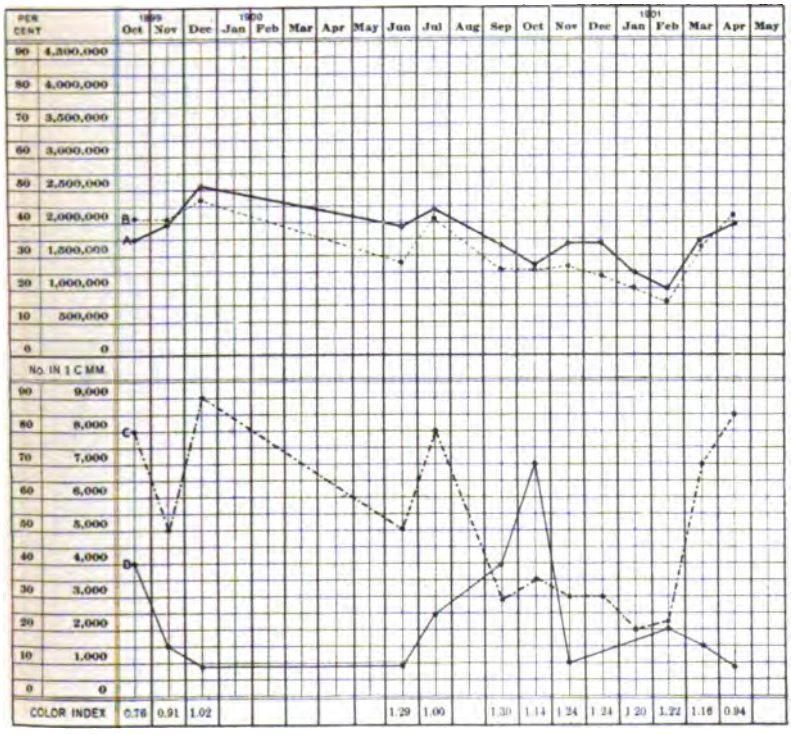
is in an improvement wave, as indicated by the accompanying chart. (Chart III.)

No. 13 of the series has been under constant observation since the report. She was upon a wave of improvement when last reported, which continued until September, 1900. Since that time there has been a decline, with slight waves of improvement, but the chart shows a continuous decline. Nucleated red cells disappeared entirely from the blood during this long wave of improvement, but have been found

during the last two months. When at the greatest height of the wave of improvement the color index was low, but with the wave of decline came the usual high color index. (Chart IV.)

The further study of these cases has brought forth nothing new in the way of blood changes. The conclusions which were read in

CHART III.



A. Hemoglobin. B. Erythrocytes. C. Leukocytes. D. Nucleated reds.

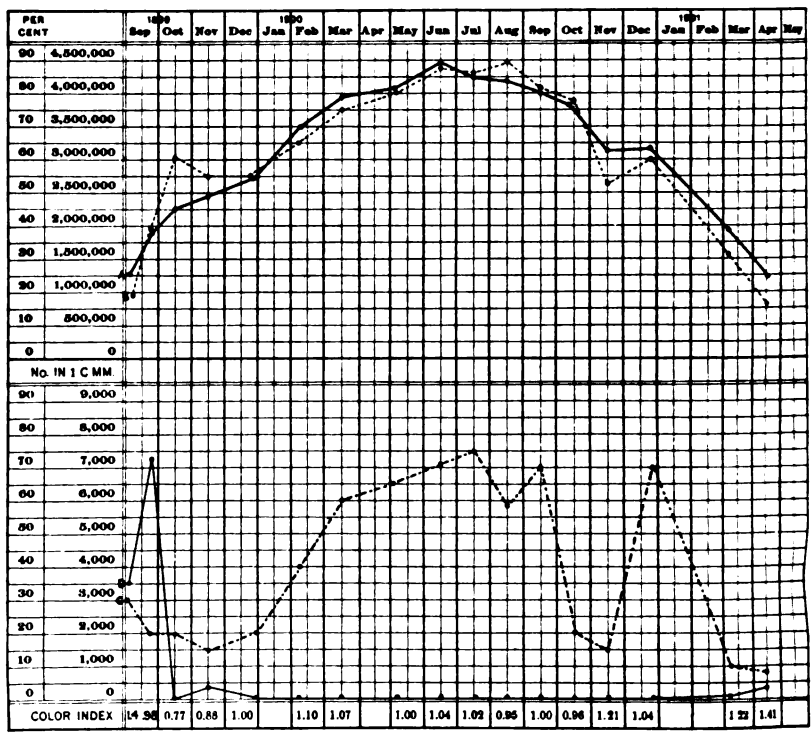
the paper of last year have been fully borne out by the continued examinations made.

Dr. Joseph A. Capps,[1] who is associated with me in my private work, has made some interesting experiments with the hematocrit during the last year.

[1] A Preliminary Report on Some Observations of Blood in Anemia. Journal of the American Medical Association, February 16, 1901.

It has long been recognized that the blood in pernicious anemia is characterized by the presence of large red cells, both nucleated and non-nucleated. This tendency to enlargement of the cells explains in part their increased capacity for taking up and carrying hemoglobin. To express accurately the actual hemoglobin content of the average cell we use the convenient term "color index," which is the

CHART IV.



A. Hemoglobin. B. Erythrocytes. C. Leukocytes. D. Nucleated reds.

percentage of hemoglobin divided by the percentage number of red cells.

The means of determining the size of the red corpuscles is quite as important as the estimation of the hemoglobin content of the cells.

The old method of measuring the diameter of a large number of cells is unsatisfactory because no account is taken of the thickness of

the cell, and we know that in this respect great variations occur. A fairly accurate result may be obtained, however, by the use of the centrifuge in connection with a red cell count. The percentage volume of the red cells as a whole, as obtained from the graduated capillary tube of the centrifuge, is divided by the percentage number of red corpuscles, which gives the percentage volume of the individual corpuscle.

For the quotient no term has hitherto been employed. The name of "volume index," therefore, is suggested as corresponding to the familiar "color index."

Thus a reading of 45 on the tube equals 90 per cent. by the hematocrit; and if in a given case the red cells number by the Thoma-Zeis count 3,750,000, or 75 per cent., then 90/75 equals 1.20 the volume index, an increase of 20 per cent. above the normal in the volume of the average cell. In twelve of the series reported this test has been applied, and all have shown a large volume index throughout the greater part of the disease. The lowest volume index was 0.93 and the highest 1.93, the others ranging from 1.05 to 1.59. In some instances the volume index was increased when the cell diameter average was not above the normal, thus indicating a probable enlargement of the cell in depth, but not in circumference.

These observations also demonstrate that the hematocrit is of value in giving us the corpuscular mass, but is unreliable for computing the number of cells.

During the year nine new cases of pernicious anemia have come under my personal observation, and have been examined frequently enough to make the diagnosis certain in each case. Of these cases seven were males and two females. The ages ranged from thirty-six to sixty-nine years. All were well-to-do people, and in no one was there any specific cause to be found to which the disease could be attributed. The observations noted last year, that in most of the cases reported gastrointestinal disturbance was a common accompaniment, has been found true also in the nine new cases. Four of the nine new cases sought consultation for gastrointestinal disturbance. In but one of the cases was a bad condition of the teeth and mouth found which could in any way be a cause of the trouble. A short account of each case will be of some value to those who desire to note the clinical course of pernicious anemia.

CASE XXI.—Mrs. R. L. S., aged fifty-one years, married, mother of five children, came under my observation November 13, 1900. Had enjoyed good health the greater part of her life. Has had "falling of the womb" the past twenty-nine years, but has not suffered much from pelvic disturbance. For ten years she has had gastrointestinal fermentation; some nausea, usually in the afternoon when over-tired. There was often a sense of weight and gnawing in the epigastrium; the appetite was usually poor; the bowels constipated. During the last few months the bowels have been loose, with one or two painless, watery stools a day.

One maternal aunt died of cancer; three maternal uncles died of tuberculosis.

Examination revealed nothing of importance in the chest. The abdomen was somewhat protuberant, and there was slight diastasis of the recti muscles. There was enteroptosis, the stomach lying well down in the lower quadrant of the abdomen. The liver edge was palpable two fingers' breadth below the costal arch. The spleen was not palpable. The stomach contents, one hour after a meal of lean meat, bread, and tea, gave no reaction for hydrochloric or other organic acids. The urine, specific gravity, 1020; no albumin, no sugar, and no sediment with the centrifuge. Blood examination: Hemoglobin, 40 per cent.; specific gravity, 1044; red cells, 1,648,000, and 7500 white cells per cubic millimeter. Nucleated red cells, with megaloblasts predominating, were present. Poikilocytosis and chromatophilia were marked.

An examination made April 23, 1901, showed some improvement: hemoglobin, 42 per cent.; specific gravity, 1045; red cells, 2,110,000, and white cells, 5500 per cubic millimeter; five megaloblasts and three normoblasts were estimated to be present in one cubic millimeter. The patient was subjectively better without a gain in weight, but still complained of the gastrointestinal fermentation and slight looseness of the bowels. The stools of this patient were not examined, because her home was a distant point, and a visit of a day only was made to Chicago on each examination. There was no perceptible cause for the disease to be found.

CASE XXII.—W. F. McC., dentist, aged thirty-six years, single, presented himself first on May 31, 1897. He stated at that time that his illness began with tingling and numbness of the fingers, which later involved the feet and legs, with tenderness of the calves and the knee-joints. No spontaneous pain. He had diarrhea for six weeks at the beginning of this illness; always had some gas and epigastric weight after eating. The urine was scant but normal, as he had himself examined it. In February, 1897, a competent hematologist had found the normal number of red cells, but hemoglobin much diminished. A diagnosis had been made in this case of multiple neuritis from intoxication due to digestive disturbance. An examination made at that time showed a man fairly well nourished; weight, 136 pounds. The chest was negative. The liver area seemed normal. The spleen was not palpable. The urine, specific gravity, 1028; urea, 1.9 per cent.; alka-

line reaction; phosphates in excess; no albumin, no sugar, no casts. There was tenderness along the posterior tibial nerves. The reflexes were not altered. Blood examination revealed hemoglobin, 40 per cent.; red cells, 2,300,000; white cells were not counted. No parasites were found in the blood.

On November 20, 1897, patient again presented himself for examination. He had been in California for three months, and was much improved in general health. He still complained of some pain along the course of the tibial nerve, and the tingling and numbness of the fingers and toes continued. Blood examination showed hemoglobin, 80 per cent.; red corpuscles, 4,000,000 per cubic millimeter. The patient was not seen again until March 5, 1900, when he again presented himself. He complained of great weakness and of lessened endurance. He looked pale, and there was a yellowish tinge of the skin. The physical findings were negative, excepting as noted above. Blood examination: Hemoglobin, 60 per cent.; 3,048,000 red cells and 10,000 white cells. There were no nucleated cells found.

On April 2, 1900, hemoglobin was 55 per cent.; red cells, 2,248,000, and white cells 6000 per cubic millimeter. Patient felt weaker than before, and complained of dyspnea upon exertion. Physical findings negative.

On April 28th there was a still further decline. Hemoglobin was 42½ per cent.; red cells, 1,448,000, and white cells 5000 per cubic millimeter. The patient was continued upon restorative tonics of arsenic and iron, and advised to go into the country. Nucleated red cells were found with megaloblasts predominating.

On December 28, 1900, the hemoglobin was 33 per cent.; specific gravity, 1039; red cells, 1,264,000, and white cells 4400 per cubic millimeter. Normoblasts and microblasts were found, and at one time megaloblasts were found. Poikilocytosis and polychromatophilia were present during these latter observations, and this condition of the corpuscles, with the continued high color index and the progressive character of the disease, make the diagnosis practically certain. The patient is at present living in the country, and no observation has been made since that last noted above. There was no perceptible cause for the disease to be found.

Case XXIII.—Mr. F. B. K., aged fifty-three years, merchant, married, American, presented himself June 29, 1900. Mother died of tuberculosis, with an associated anemia; father died of heart disease. Patient has not used tobacco or alcohol during his life, and has always been a healthy man. He has not overworked, but has lived much of the time indoors. A year ago he began to lose strength, and later on lost somewhat in weight. Six months later he and his friends noticed a pallor, and he had some dizziness and shortness of breath upon exertion. During the last two or three months there have been numbness and tingling of the extremities. His main complaint at present is weakness, with shortness of breath, and palpitation of the heart with exercise or excitement. He is restless, emotional, and is faint at times. There has been swelling of the lower extremities for several weeks,

especially in the latter part of the day. He has noticed some black and blue spots on the thighs recently. His appetite is variable; there is no indigestion; bowels are usually constipated. Occasionally there has been diarrhea recently. His weight a year ago was 197 pounds, and in January, 1900, 165 pounds, and at present 158 pounds. He has noticed no blood in the stools; has no epistaxis or hemorrhage from the gums.

On examination a marked pallor, with a lemon-yellow tint, is very noticeable. The mucous membranes of the lips and mouth are yellowish pale. The teeth are good; the mouth is clean; there is some puffiness of the eyelids. The eyes are normal, including the retinæ. The pulse is small and rather rapid. There is a capillary pulse in the lips. The heart area is normal; the lungs are negative. There is a systolic bruit in the neck. The abdomen is negative; the rectum is negative. The reflexes are normal. Urine, specific gravity, 1013, acid reaction; 0.6 of 1 per cent. albumin, with a few finely granular and hyaline casts present. Blood examination: Hemoglobin, 28 per cent.; specific gravity, 1038; red cells, 1,006,000, and white cells 1500 per cubic millimeter. Poikilocytosis is very marked. Many nucleated cells are found with a preponderance of megaloblasts. Color index in this case is very high—1.53.

A letter of recent date from a physician states that the patient improved for a few months, but is now becoming rapidly worse again. There was no perceptible cause for the disease to be found.

Case XXIV.—W. J. F., aged forty years, male, merchant, presented himself November 10, 1900, with a letter from his physician, Dr. Kanne, of Peoria, Illinois. His father died of blood-poisoning; mother living at the age of seventy-two years. Patient gives a history of good health, except for typhoid fever when eighteen years of age. He is an active worker. Denies venereal disease. While at West Baden, Indiana, September, 1898, he was taken with a severe diarrhea which lasted for about two weeks. This was accompanied by pain and slight fever. Succeeding this he was weak and debilitated, and has never been well since that time. A year ago it was noticed that his skin was pale and of a yellowish tint. There was some loss of weight at this time, with diminished strength and endurance, and noticeable dyspnea upon exertion. While at Eureka Springs, Ark., he gained fifteen pounds, and has since retained about the normal weight—142 pounds. During the last two months he has noticed that the pallor has increased; he has lost strength; has attacks of dizziness, faintness, and shorteness of breath upon exertion. Slight swelling of the ankles has occurred in the latter part of the day. There has been slight headache occasionally, and there is some numbness of the toes and of the finger-tips.

Examination shows a man of about normal weight for his height; skin is pale, and of a lemon-yellow color. Mucous membranes of the mouth and pharynx very pale. There are some palpable glands in the superficial carotid triangles. The teeth are sound; the gums are normal; the lungs are negative; heart area is normal, tones clear; the pulmonic second sound slightly

accentuated. Liver and spleen negative. Knee-jerks are active. There is an ankle clonus of slight degree present; a slight edema of the ankles. The rectum is normal; the eye-grounds are normal; urine, specific gravity, 1015; no albumin, no sugar, no casts. Blood examination: Hemoglobin, 43 per cent.; red cells, 1,512,000, and white cells 6400 per cubic millimeter. Many nucleated cells present, with a preponderance of megaloblasts.

Many examinations of the blood had been made by Dr. Kanne, which agreed, in the main, in the relation of the hemogobin to the red cells, with the examination noted above.

A letter of recent date from Dr. Kanne states that the patient was at that time upon a wave of decline. There was no perceptible cause for the disease to be found.

CASE XXV.—J. K., aged fifty-six years, male, married, merchant, presented himself November 24, 1900. Family history is negative; brothers and sisters are healthy. The patient has always been a healthy man in active business. He has used alcoholic drinks very moderately. A year ago he noticed a little numbness in the hands and feet, which has since remained. Six months ago his wife noticed that he was pale, and since then there has been an increase of the pallor, with weakness, lessened endurance, shortness of breath upon exertion, and dizziness and faintness at times. The appetite has become poor, and digestion disturbed by gas, with eructation, and a sense of weight and distention in the epigastrium. He has been drowsy, but at times very nervous. He has not lost in weight.

Examination shows a well-nourished man, with a skin very pale and yellow; mucous membranes white. The teeth are good; the lungs are negative; the heart tones are normal, and the heart area is not increased. The liver extends three inches below the costal arch in the mammary line. The spleen is palpable two inches beyond the costal margin. The stomach and intestines are negative; the rectum is negative. There is light edema of the ankles; the knee-jerks are present and active. Urine, specific gravity, 1021; no albumin, no sugar, no casts. Examination of the blood: Hemoglobin, 34 per cent.; specific gravity, 1038; red cells, 1,653,000, and white cells 2200 per cubic millimeter. Nucleated cells were found with megaloblasts in preponderance.

Examination of the blood made December 13, 1900, by Dr. Werner, of Quincy, Illinois: Hemoglobin, 33 per cent.; red cells, 1,626,000, and whites 2100 per cubic millimeter, with nucleated red cells, including megaloblasts. Poikilocytosis was very marked in this case, and the megaloblasts were noticeable because of the marked fragmentation of the nuclei. There was no perceptible cause for the disease to be found.

CASE XXVI.—J. E. P., aged sixty-nine years, married, manufacturer, came on January 7, 1901. His mother died of tuberculosis; no other history of inherited disease in the family. The patient has practically abstained from alcohol and tobacco. Had typhoid fever at the age of twenty-eight. He can recall no other serious illness. Four months ago he was troubled

for several weeks with nausea and dizziness, burning sensation in the stomach, with eructations of gas, and hot sensations in his throat. Six weeks ago there were nausea and faintness, with water-brash. With this there has been progressive weakness, with loss of flesh and pallor, shortness of breath, and increasing lack of endurance. There have been some numbness and tingling in the fingers and toes. He vomited once and ejected food which he had taken eight hours before. He has never noticed blood in the stools. He has had no noticeable loss in weight.

Examination shows a rather thin man, weight 140 pounds; maximum weight, 158 pounds; skin is very pale and of a yellowish tint. The tongue and mouth are clean; the molars are gone, but the remaining teeth are sound. There is a thickening of the palpable arteries; there is a capillary pulse in the lips. The lungs are negative; the heart dulness appears normal; there is a soft systolic blow over the aortic area. The liver edge is felt on inspiration somewhat sharp; spleen is not palpable. There is a double inguinal hernia; the rectum is negative. Urine, specific gravity, 1015; reaction, acid; no albumin, no blood, no casts. Blood examination: Hemoglobin, 39 per cent.; specific gravity, 1043; red cells, 1,538,000, and white cells 2500 per cubic millimeter. Many nucleated cells were found, including megaloblasts.

The patient was placed upon a restorative tonic treatment. On February 8, 1901, a month later, blood examination gave hemoglobin, 56 per cent.; specific gravity, 1050; reds, 3,194,000, and whites 5000 per cubic millimeter. Nucleated cells were present, and poikilocytosis was marked. This noticeable improvement of the blood was accompanied with a corresponding subjective improvement.

On March 26, 1901, blood examination showed 78 per cent. hemoglobin; specific gravity, 1056; red cells, 3,768,000, and white cells 6000 per cubic millimeter. He had gained in strength; his digestive power was good; and in every way felt himself almost well. The restorative tonic treatment was continued.

A letter from the patient, written about the middle of April, states that he is not now so well. That he suffers from weakness, shortness of breath upon exertion, and that his color is not as good as it was when he was last examined.

The improvement wave in this case occurred coincidently with the restorative tonic treatment, and at first sight it would seem that the treatment had something to do with the great improvement; but the observations made in the past upon the other cases have been so contradictory that one cannot but feel that improvement may take place in these cases without the aid of restorative tonics, and that in some instances at least remedies have received credit in pernicious anemia, when in all probability it was the natural course of the dis-

ease which brought about the improvement, and not the drugs used. There was no perceptible cause to be found for the disease.

CASE XXVIII.—Mr. W., aged sixty years, married, lawyer, presented himself September 23, 1900. He states that his previous health has been good, but that he has lived a life of care and anxiety. The last few years he has been at work upon a patent which he believed was worth a fortune, and recently arrangements were made for its adoption by a syndicate, which has brought him increasing care and anxiety, so that he has not had much rest either day or night. Three months ago he noticed that he was not as strong as usual, and that his endurance was less. He had shortness of breath upon exertion, and there was a good deal of palpitation of the heart. The extremities became cold, especially when excited, and there was tingling of the finger-tips and toes. His digestion was poor, and there was a good deal of fermentation, with eructations of gas. The bowels were usually constipated. He had noticed but little loss of flesh. His friends noticed that he was pale.

On examination: six feet in height, well nourished, skin very pale, and of a lemon-yellow tint. Mucous membranes of the mouth were pale; the teeth in fairly good condition; the gums healthy; the lungs negative; the heart area normal. A murmur was heard in the neck when the patient was lying down, and a soft systolic murmur was heard at the base and apex of the heart. The liver was apparently normal in size; the spleen was not palpable; the rectum was negative; urine was negative. Blood examination: Hemoglobin, 22 per cent.; red cells, 1,388,000, and white cells 6000 per cubic millimeter. There were many nucleated red cells, megaloblasts predominating three to one over the normoblasts. There was marked poikilocytosis. Several other blood examinations were made, which confirmed the primary examination.

The patient continued under observation for about two weeks, remaining practically in the same state, but with the addition of an edema of the lower extremities gradually increasing in severity. He was obliged to go East at this time, and died suddenly in Boston, on November 7th. An autopsy was not performed. There was no perceptible cause for the disease to be found.

CASE XXIX. is an important and most instructive one, and is reported in detail with the postmortem findings, including a microscopic examination of the different tissues of the body. Mrs. V. J., aged thirty-nine years, married, mother of four children, came to the Presbyterian Hospital, Chicago, on July 26, 1900. Her father is living, and has had stomach trouble a good deal of his life. Her mother died of paralysis. A maternal aunt died of cancer. There is one brother and seven sisters, all living and in good health. The patient has been obliged to work hard all her life, and has not been in good health since the birth of her last child. Two of her children are living and two are dead. One was still-born. The patient had typhoid fever when she was young, and suffered from malarial fever, as it was told

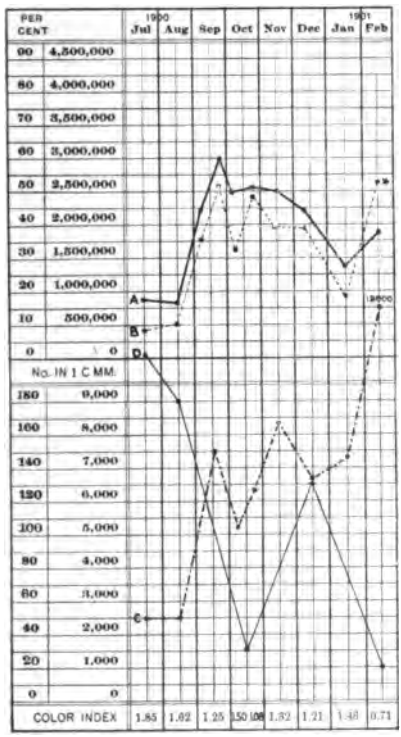
her, two years ago. Her present illness began after the birth of her last child, seven years ago. There was indigestion, with gaseous eructations, acidity, fulness and weight in the epigastrium after eating. Occasionally there was vomiting, but the vomiting had no relation to the meals. She never vomited blood. On several occasions she vomited bile after repeated attacks of vomiting. The appetite has been variable on the whole, but had been often good. There was diarrhea with watery stools containing undigested food for the first six years of her illness.

A year ago she commenced Christian Science treatment, and after six months the diarrhea ceased and she became much better. Recently there has been a good deal of irritation of the bladder, with a desire to urinate frequently. There has been a sense of pressure about the rectum, and at times some pain, especially if the bowels were constipated. There has been some difficulty in getting the bowels to move, because of a sense of numbness in the rectum in the last few weeks. Menstruation ceased four months ago; the flow was scant for a month or two preceding the cessation. Strength and endurance have been gradually lost. She was overworked during most of the illness, but her legs became, finally, so weak that she was obliged to remain in bed on and after December, 1899. She and her friends noticed that she was paler than usual and that the skin had a yellowish tinge. This has increased since she has been in bed. She has noticed that her legs have become much weaker since she went to bed, and that she has not complete control of the bladder. The bowels have usually been constipated, and required a laxative or the injection of water into the bowel to move them.

Examination showed a woman fairly well nourished; the skin was very pale and of a distinct yellowish tint. The mucous membranes of the lips and mouth were pale. The tongue was indented and furred. There were no carious teeth; the lungs were negative. The heart area was normal. There was a soft systolic blow in the mitral and pulmonic areas. The radial pulse was about 100 per minute, small and soft. There was diastasis of the recti abdominalis muscles. The belly was "pot formed." There was very palpaple visceroptosis, including the liver, kidneys, spleen, intestines, and stomach. The uterus was retroverted and moderately fixed. Some pain was caused by an attempt to restore it to the normal position. The body of the uterus was small, and a small nodule was felt in its posterior surface. The rectum was normal; the eye-grounds were normal. The patient had abrasions of the skin over the sacrum, and lay partly upon the side, with the thighs and legs flexed. There was some atrophy of the muscles of the lower extremities, chiefly of the extensor groups. The knee-jerk was increased. There was a slight ankle clonus, more marked in the left than in the right foot. Babinsky's sign was present in the right, but not in the left. Sensation was diminished in the lower extremities, most marked in the feet and legs, and almost normal in the thighs. Muscular sense was noticeably absent. The patient could perceive pain, and in certain areas of the leg could distinguish heat from cold, but in others heat was felt as pain, and cold

was felt as a touch only. There was a small area in the left inguinal region and upon the outer surface of the right thigh, where tactile sense was diminished and heat was felt as pain. There was noticeable loss of power in the legs and thighs, which was more marked in the right than in the left. There was loss of power in the rectum and bladder. The muscular power and the sensation of the skin in the upper extremities seemed normal. The patient complained of a sense of constriction about the abdomen, beginning at the waist-line. The urine, specific gravity, 1012; acid reaction; no

CHART V.



A. Hemoglobin. B. Erythrocytes. C. Leukocytes. D. Nucleated reds. * Death.

albumin, no sugar, and microscopically negative. Blood examination: Hemoglobin, 20 per cent.; red cells, 610,000, and white cells 3200 per cubic millimeter. Poikilocytosis was very marked, and nucleated red cells, with megaloblasts predominating, were found. (Chart V.).

The patient remained in the hospital steadily from that time until the date of her death, on February 27, 1901. Many blood examinations were made, as indicated in the accompanying chart, which showed two waves of improve-

ment while under observation, and the death of the patient occurred during the last wave of improvement. The blood findings were in every way all characteristic of pernicious anemia. The interesting point in the case is the spinal-cord involvement, which consisted of a paraparesis, noted at the time of admission, and which gradually increased up to the time of her death. There was finally complete paralysis of the bladder, and in consequence thereof infection which extended into the kidney, and the patient died of septicemia dependent upon a pyelonephrosis. This was possibly aggravated by extensive bed-sores, which increased in extent and depth in spite of the greatest care.

The stomach contents were examined after test-meals on several occasions, and hydrochloric acid was found absent in every instance. The stools were examined, and were found negative as to parasites. The urine, after the infection of the bladder, became alkaline, and contained a good deal of pus and many bacteria. The character of the bacterial infection was not discovered. During the greater part of the illness the temperature of the patient ran an irregular course of either a remittent or an intermittent type, but it was never severe in degree. The pulse was usually rapid and small, and there was always a complaint of great weakness and breathlessness upon exertion. The nourishment of the patient remained good throughout the whole illness. Her appetite was usually good, and, although digestion was not perfect, assimilation of the food occurred. About the middle of January, 1901, infection of the bladder and of the kidneys occurred, and from that time on the patient suffered from a remittent and intermittent type of fever of severe degree, and at times was delirious, in consequence apparently of the fever. Five days before death the temperature fell below normal, and remained so until death, and for two days preceding the demise it registered from 93° to 94° F. in the rectum. The pulse and respiration fell with the temperature, and the patient died with a very low temperature, slow pulse, and slow respiration. At the time of death the blood findings indicated a wave of improvement, and just at death there was a terminal leukocytosis.

The postmortem examination was made by Professor Hektoen at the Presbyterian Hospital on February 27, 1901, when the following postmortem diagnosis was made: General anemia; red marrow in femur; splenic hyperplasia; degeneration of posterior columns of spinal cord; ascending cysto-uretero-pyelonephritis, with necrosis of the medullary papillæ; bronchopneumonia; fatty liver; thrombosis, with softening of inferior vena cava and continuations to the left of the renal vein; sclerosis of aorta; chronic pelvic peritonitis, with tubo-ovarian adhesions; extensive sacral decubitus; edema of feet.

The body, which is still warm, is that of a rather middle-aged, poorly-nourished woman. There is no rigor mortis, and no posterior lividity. There are huge bed-sores, with great undermining of skin over sacrum, exposing the coccyx and lower part of the sacrum and the left trochanter.

The limbs are fixed; the knees somewhat flexed, and the feet, especially the left one, slightly edematous. The sclerotic coats, especially that of the left eye, show traces of recent hemorrhage.

The abdominal cavity is empty, and peritoneum smooth. The pleural cavities are empty and smooth. Mucous membrane of the gums is intact. The tongue, in its anterior roof, shows branching fissures; its mucous membrane, as well as that of the pharynx, esophagus, larynx, and trachea, is normal. Peribronchial glands normal. The lungs are pinkish externally, and but little pigmented; they are soft, spongy, and crepitant. The cut surface is pinkish and bloodless. In the lower lobe of the right lung there are several areas of recent lobular consolidation, from which a thin, purulent fluid can be expressed. In this lobe the bronchi also contain mucopus. In the upper lobe there are one or two small, black, subpleural concrements.

The heart weighs 250 grams. There is a considerable amount of subepicardial fat. The cavities are somewhat dilated, and contain a small amount of fluid blood; their walls are thin and flabby; myocardium is normal. In the left ventricle there is an aberrant tendinous cord, which crosses the cavity in the lower half. There is no evidence of fatty degeneration in the myocardium. The beginning of the pulmonary artery is smooth. The right shows several yellowish areas, the largest one being in its descending portion. There is an obliterating thrombus of the inferior vena cava, beginning opposite the fourth lumbar vertebra and extending downward to the iliac veins and the right side into the femoral vein and its branches almost to the knee. The thrombus in the left iliac vein is red, in places grayish, with extensive puruloid softening.

The spleen weighs 350 grams; its external surface is smooth and of slaty color; the capsule does not wrinkle. The cut surface is of true reddish-gray color; its consistence is quite firm, its connective tissue being visibly increased. The Malpighian bodies are not visible except in a few places.

The liver weighs 1800 grams. There are a few perihepatic adhesions binding it to the diaphragm. It is yellowish in color, both externally and on the cut surface. On section the peripheral parts of the lobules appear much yellower than the central portions. The bile passages are patent. The gall-bladder contains a quantity of very thick, viscid, tarry bile, and a number of small, faceted calculi.

The pancreas is normal in size, and appears normal on its cut surface.

The stomach is small and contracted; its mucous membrane was not examined. The stomach was filled with formalin for histologic purposes. Mucous membrane of the small intestine is intact, and apparently not greatly atrophic; that of the large intestine and rectum is normal. The vermiform appendix is also normal.

The kidneys are enlarged, weighing together 520 grams. Their external surfaces, particularly that of the right, show roughening of the capsule, with yellowish spots, some of them purulent. The pelvis of each is filled with turbid, thick pus, in which there are many necrotic masses. Mucous

membrane of the pelvis is thick, and, in places, ulcerated and irregular. The apices of some of the medullary pyramids are distinctly necrotic, being capped by a yellowish, rather firmly adherent eschar. In some places this has fallen off, leaving ulcers. The calices appear dilated, and lines of suppuration extend upward into the medullary pyramids and into the cortex. In the pelvis of the left kidney there is a firm, yellowish, adherent thrombus in the branches of the renal vein. The ureters are thickened and somewhat dilated; their mucous membrane is roughened and covered with pus. The urinary bladder is contracted, and its walls thicker than normal. Its cavity contains a small quantity of turbid fluid. The mucosa is roughened, and in places is diffusely red and hemorrhagic.

The right ovary and tube are small and shrunken and embedded in adhesions. There are adhesions about the left ovary and tube, among which there is quite a large collection of serous fluid. The uterus is about normal in size. Its mucous membrane is smooth. There is a bilateral, old cervical tear. The vagina is normal.

The skull and membranes of the brain are normal. There is an excess of cerebrospinal fluid; in the lower part of the spinal cord there are numerous minute, bony white scales in the meshes of the pia-arachnoid. The cord is about uniform in consistency throughout. On cut section there is distinct degeneration in the posterior internal columns. In the lower part of the cord this degenerated area becomes wider and more irregular.

The marrow of the left femur is deeply red throughout and quite cellular. Smears contain megaloblasts, normoblasts, etc.

Histologic examination made by Mr. Robinson in the laboratory of Professor Ludvig Hektoen and by Dr. J. F. Smith, of the house staff of the Presbyterian Hospital:

Lungs. Sections from the more solid portions of the lungs showed marked degeneration; quite extensive destruction of the alveolar walls, with the alveolar spaces of the large portion of them completely filled by disintegrating leukocytes and a serous transudation. In the remaining part the consolidation is much less complete. The alveoli are occupied and the character of the material within them somewhat different, the serous portion being much more abundant, and the leukocytes fewer in number. A considerable amount of blood can be seen along the lines of the broken alveolar walls in the denser portions of the sections. The smaller capillary vessels also are highly congested, and the large vessels, whose walls show evidence of degeneration in their granular and fragmentary appearance, are distended with serous material.

Heart. The muscular fibers under high power of the microscope present a peculiar appearance. Along the margins the protoplasm appears normal, with its transverse striations distinctly visible, while the central portion in many places is pale and degenerated, and shows no transverse striations. This gives to the fibers somewhat the appearance of a separation into two longitudinal divisions. Many of the fibers show a longitudinal splitting into

fine threads. The nuclei stain well, but the protoplasm throughout shows some irregularity on staining. Bands of light color cross the fibers transversely. Many of the nuclei are large and irregular.

Femoral Vein. Sections of this vessel show the wall varying considerably in thickness in different portions, containing but a scant amount of muscular tissue. The lumen is occupied by a large mass of fibrin and disintegrated blood, the central part of which is less dense and more granular, being composed largely of degenerated cellular elements. Around the margins of the mass some evidence of proliferation of the fixed tissue cells is seen, and in a few places there are growths starting inward from the vessel wall. No bacteria can be found in sections stained by Gram's method.

Spleen. The Malpighian bodies are very indistinct throughout the greater portion of the section, and in some places entirely invisible. The splenic tissue in all parts of the section is greatly obscured by the presence of an enormous amount of blood. The nuclei of the cells were visible, stained quite deeply, but their protoplasm is pale. The capsule of the organ is thickened, and the connective tissue within is notably increased in amount, but has a peculiar granular, disintegrated appearance, which is seen also in the walls of the vessels included within the larger trabeculæ. The bloodvessels show some increase in thickness of their walls, and the lumens, in most instances, are engorged with blood. The elastic-tissue fibers are much increased, as shown by Weigert's special stain.

Liver. Sections of the liver show extensive fatty degeneration, particularly in the peripheral portion of the lobules, where the liver cells are almost entirely replaced by fat vacuoles. Only a very scanty amount of protoplasm and a few poorly stained nuclei remain. Immediately surrounding the central vein of the lobule there is in most cases a small area of liver tissue, almost free from fat, showing, however, evidences of degeneration by the dull color and granular character of its protoplasm, pale staining of the nuclei, and the presence of some granular detritus in the spaces between the cell columns. The capsule of the organ is not thickened, nor is the interlobular connective tissue apparently increased in amount. The bile ducts are not proliferated. Some of them are large and have wide lumens. The bloodvessel walls show no particular changes; the lumens are occupied by varied amounts of true blood. Staining with ferrocyanide shows small amounts of granular iron here and there in the interstitial tissues. Staining by Adami's carbolthionin method shows many diplococcus-like bodies located within and between the liver cells.

Pancreas. Sections of this organ stain well, and show no apparent abnormality more than a congestion of some of the smaller bloodvessels, and perhaps a slight increase in the thickness of their walls. The lobules are distinctly marked off. Numerous bodies of Langerhans of various size are present throughout the section.

Stomach. Sections of the fundal portion of the stomach show marked thinning of its wall, particularly of its mucous and muscular layers. The

glands of the mucosa are few, shallow, atypical, and the epithelial cells of their lining are very indistinctly marked off and poorly stained. Round-cell infiltration is present. The submucous layer is comparatively thick. Most of its vessels are congested. The muscular layers are thin and pale. Practically the same may be said of sections very near the middle of the lesser curvature of the organ. Muscular tissue, however, is more abundant, and the thickened vessel walls in the submucosa are more evident. In sections from near the pylorus atrophic changes are not seen. Mucosa is normal in thickness and appearance, and the muscular layers are white, dense, and well stained. On the inner surface and in the lumens of the more superficial glands are seen bacterial colonies.

Intestines. The intestinal tract in its upper portion—that is, the duodenum and jejuno-ileum—shows no marked pathologic change. Walls of the ileum, particularly in the region of the cecum, are rather atrophic, especially its mucous layer, which in places is reduced to a narrow band, with but slight resemblance to mucosa. There is diffuse, round-celled infiltration of the mucosa. The submucosa in places is congested and edematous. Numerous mast cells are seen in the submucous layer.

Kidneys. Sections of the kidney show marked destructive changes toward the apices of the pyramids. The surface bordering on the pelvis is composed of typical granulation tissue infiltrated by large numbers of polymorphonuclear leukocytes. There is diffuse, almost universal edema and leukocytic infiltration of the somewhat increased interstitial tissue, and congestion of the capillary and larger vessels. Throughout the section are granular necrotic areas of variable size, and minute abscesses. A large portion of the tubules in both pyramidal and cortical portions are dilated and packed with masses of polymorphonuclear leukocytes embedded in a granular débris. In many places the cells have undergone complete necrosis, involving also the lining epithelium and peritubular connective tissue. The straight tubules, even where densely packed, often have an intact epithelium with clear nuclei. In others it is flattened, degenerate, or necrotic. The glomeruli have somewhat thickened capsules and are much congested. Others yet show carious degenerative changes, not a few being entirely necrotic and granular. In some places glomeruli and tubular contents have dropped away during the handling of the sections, leaving only the thickened connective tissue framework.

Spinal Cord. Sections of the cord, stained by the Weigert-Pal method, show degenerative changes, with absence of myelin sheaths from many of the tracts, at some levels comparatively few sheaths are present in any part of the transverse section, and their absence from the posteromedian and crossed pyramidal tracts is more or less complete at all of the levels examined.

Bacteriologic Examination. Media inoculated from the heart's blood showed no gross changes, either by aërobic or anaërobic methods of cultivation. No cultures were obtained from the lungs. Upon an agar slant inoculated at the autopsy from the thrombosed femoral vein there developed a pure

culture of bacillus coli communis. Upon agar-agar plates from the liver there appeared a number of small, white colonies composed of small cocci, which, stained by Gram's method, produced a moist, whitish growth on glycerin agar, a dirty brownish-white growth with discoloration on potato, no apparent change in litmus milk, no gas in glucose agar, and no liquefaction of gelatin. From the kidney were obtained cultures of small cocci which stained by Gram's method, and in subcultures produced gross characteristic staphylococcus albus, also small, bluish-white colonies of small oval bacilli, which were almost completely decolorized by Gram's method of staining, produced a scanty, moist growth upon the surface of glycerin agar, a brownish growth with discoloration on potato, gas in glucose agar, apparently no alkalinity on litmus milk, and a funnel-shaped liquefaction of gelatin.

It was intended to give illustrations of sections of the spinal cord at different heights to show the site of the degenerative changes in the cord. Sections made of the medulla and pons show degeneration of certain tracts here as well as in the cord, and it, therefore, seems wiser to postpone the report upon the histology of the cord until a more extended examination may be made including the entire cerebro-spinal system. This will be the subject of a future report to the Association.

The changes in the spinal cord in this case are the same apparently as those reported by others, and consist of degeneration in the postero-median, the pyramidal, the direct cerebellar, and Gowers' tracts. Diffuse degeneration appears in this case in the cervical and upper dorsal cord. It seems, therefore, in this case that while the degenerative changes are limited to certain columns in some parts of the cord, especially in the lumbar, dorsal, and upper cervical, it becomes more diffuse, as noted above, in other portions of the cord. One of the peculiar conditions noted is the absence of shrinkage in the degenerated tracts. Possibly this may be due to the shorter course of the disease as compared with the more chronic cord lesions of locomotor ataxia, lateral sclerosis, etc.

FURTHER NOTES OF A CASE OF PERNICIOUS ANEMIA REPORTED AT THE MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS IN 1900.

WITH REMARKS ON THE DIAGNOSIS OF THE DISEASE.

By FREDERICK P. HENRY, M.D.,
OF PHILADELPHIA.

At the meeting of the Association in 1900 I reported five cases of pernicious anemia, each of which possessed features of unusual clinical interest, and made some remarks upon the diagnosis of the disease and the characteristic alterations of the blood which it presents. Exception was taken to one of my cases (Case IV.[1]) on the ground that nucleated red cells, and especially megaloblasts, had never been found in the blood of the patient In reply to my question as to how my critic would classify such a case as I reported, he said that he "should regard it as a case of secondary anemia of unknown origin."[2] He also stated that he had "had a number of such cases ending in recovery,"[3] but saw no reason to regard them as cases of pernicious anemia. I will not stop to discuss the question whether, with our present knowledge, pernicious anemia may not be defined as a "secondary anemia of unknown origin," but will again refer to the implication that such cases as my Case IV. are by no means rare.

I will now briefly relate the main clinical features of the case whose progress I am reporting. In vol. xv. of the Transactions its caption is as follows: "Case IV. Under observation six years, during which there have been several slight and two severe relapses, chronic gastrointestinal catarrh, with marked exacerbations preceding and during the relapses; complete restoration to health."

[1] Transactions of the Association of American Physicians, vol. xv. p. 352.
[2] Loc. cit, p. 366.
[3] Loc. cit., p. 362.

In the extreme reduction of the red cells (to 1,237,500 per cubic millimeter—*i. e.*, to about 25 per cent. of the normal) the increased percentage (30) of hemoglobin, the hypoleukocytosis, and poikilocytosis, as well as in the symptoms both positive and negative, the case was a typical one of pernicious anemia. At the time of my report last year the patient considered himself in the best of health, and his general appearance was "indicative of vigor and activity." The recent history of the case is as follows:

"I was asked to see the patient in consultation with Dr. L. D. Judd on March 29, 1901, and found him in a state of profound anemia. I found that he had been progressively failing in strength; in other words, becoming more and more anemic during the autumn of 1900, and that in December he had had another attack of erysipelas. A week before I saw him he had returned from a visit to Atlantic City, where he had been under the care of Dr. Philip Marvel, who, on February 27th, had examined his blood with the following result: Number of red cells per cm., 1,240,000; hemoglobin, 32 per cent.; white cells, 3000 per cm.; marked poikilocytosis. A differential count was not made, nor is anything said in the report concerning nucleated red cells. These figures are almost precisely identical with those of a count I made on February 3, 1894. On one of my visits in March of the present year I made several cover-glass preparations and sent them to Dr. L. N. Boston, who reported the presence both of normoblasts and megaloblasts. Under the use of arsenic and iron the patient is steadily improving, although his urine contains a considerable quantity of albumin. This albuminuria was a feature also of the last relapse, but disappeared *pari passu* with improvement in health and strength."

I presume that no member of the Association has now any doubt that this is a typical case of pernicious anemia, although, in my opinion, there never should have been the slightest question concerning the diagnosis. The demonstration of megaloblasts in the blood was not at all necessary to confirm it. There is a tendency at the present time to regard the presence of these cells in the blood as the sole criterion of pernicious anemia. According to this view, a case may present symptoms and signs and blood changes such as are not found united in any disease except pernicious anemia, and yet if megaloblasts are not detected in the blood the diagnosis of

pernicious anemia is unwarranted. Such a doctrine appears to me as pernicious as the disease to which it is applied, and for the following reasons: First, because, as already stated, the symptoms and signs, both positive and negative, and the blood changes of pernicious anemia, apart from the presence of nucleated cells, distinguish it sharply from all other diseases. Secondly, because nucleated cells, whether large or small, are not pathognomonic of pernicious anemia. A symptom or sign to be pathognomonic must fulfil one of the requirements of a specific germ—*i. e.*, it must occur in association with but one disease. Now, this is not the case with the cells called megaloblasts, which are found in leukemia, in bothriocephalus-anemia, and occasionally, though very rarely, in cases of carcinoma ventriculi and syphilis.[1] If the presence of megaloblasts in the blood were pathognomonic of pernicious anemia, the diagnosis of that disease could be made more accurately in the laboratory than at the bedside. Now, this is by no means the case, for it is impossible for the histologist to distinguish a specimen of blood from a case of bothriocephalus-anemia from one derived from a case of that mysterious disease so well styled by Birch-Hirschfeld cryptogenetic anemia.

The diagnosis of pernicious anemia is most firmly based upon the *tout ensemble* of signs and symptoms, both positive and negative. The presence of megaloblasts is confirmatory of, but not indispensable to, the diagnosis. They possess a prognostic rather than a diagnostic value, for they often appear in the blood in large numbers shortly before death, and often are absent for months during periods of remission.[2]

With reference to the statement[3] that cases of anemia with a hemic unit of 25 and a hemoglobin percentage of 30 are not rare (they cannot be rare if any individual has seen "a number" of them), and that they often end in recovery, I can only say that in a continuous service in large hospitals dating from 1874, during which time I have been on the alert for cases of pernicious anemia and conditions resembling it, I have had no such experience.

[1] Ehrlich and Lazarus, die Anæmie. Nothnagel's Specielle Pathologie und Therapie. I. Abtheilung, S. 41.

[2] Lazarus, die Anæmie. Nothnagel's Specielle Pathologie und Therapie. II. Abtheilung, S. 113.

[3] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, vol. xv. p. 362.

DISCUSSION.

DR. PUTNAM: I would like to say a word in regard to the spinal-cord changes in pernicious anemia, as I have been much interested in that matter for a number of years, and have recently reported a number of cases in connection with Dr. E. W. Taylor, of Boston. The question I wish to raise is whether the changes met with in these cases are really of a specific sort, or whether they are similar to changes found in somewhat analogous cases without pernicious anemia. If they are essential and peculiar to pernicious anemia we might suppose them to be due to the same cause as pernicious anemia, to some special poison, perhaps. On the other hand, it seems to be generally conceded that they are not due to anemia as such.

The other class of cases to which I allude are those of which I reported eight cases some ten years ago, in which conditions of malnutrition are present as a rule, but in which there is no pernicious anemia, strictly speaking. Some of these cases run on for ten or twelve years. Dr. Risien Russell and Dr. Batten, of London, have recently published an account of this second group of spinal cases, which they consider quite distinct from pernicious anemia, and Bastianelli takes a similar view.

The photographs passed around of these sections of the spinal cord show the peculiar tendency to the formation of large vacuole spaces on the peripheral portions of the older lesions, which are characteristic and seem to indicate a rapidly progressive process toward the last.

The statement was made that the posterior root areas were the ones particularly affected. If that is so, these cases differ from most other cases that have been reported. The changes, as a rule, have been scattered, and have usually corresponded to vascular areas rather than to nerve-root areas, whereas the latter distribution is characteristic of tabes.

Reference was made to Adami's work in this connection. This paper has interested me also very much. He alludes to the possibility of intestinal bacterial toxic action possibly giving rise to fibroid changes beside the changes in the liver and blood, and I wonder very much whether these changes in the spinal cord can be considered under that head.

DR. OSLER: May I call attention to one group of cases that seems to require additional study. You know the group in which there are no spinal symptoms during life, but in which the lesions are found after death, and a second group in which the spinal symptoms are noted during life. Those two groups are well known, but the third group, to which Russell has called attention, particularly the cases in which the anemia occurs subsequent to the onset of spinal symptoms, but which anemia is not regarded as pernicious, has not been studied in this country. At the National Hospital for Paralytics and Epileptics, Russell always has three or four such cases under observation.

DR. MCPHEDRAN: In regard to the third group of which Dr. Osler has spoken, I observed an interesting case last week. It was a case of very marked chronic anemia, but not pernicious, following nerve symptoms, the first of which was a universal anesthesia, which became so marked that the patient could not, for instance, determine the taste of sugar until he had sucked it for some time. The condition was not, however, a true anesthesia, but merely delayed sensation. Following the anesthesia there were paralytic symptoms, especially affecting the lower extremities.

DR. SHATTUCK: I saw this winter a case of pernicious anemia following and apparently due to nervous shock. The son of a previously healthy woman was fatally shot July 4, 1900. He was her favorite son, and the legal question has been raised as to whether the shooting was accidental or not. She has grieved deeply, and now suffers from typical pernicious anemia.

DR. MUSSER: I have here the notes of a case of pernicious anemia which probably belongs to the third group mentioned by Dr. Osler. The patient has been under observation since 1896, and when she first came had the characteristic symptoms of locomotor ataxia, which has since been followed by pernicious anemia. Prior to and during the development of the latter she had gastric crises, probably from the ataxia. She has been under the care of a number of other physicians from time to time, and among others Dr. Tyson saw her about a year ago. In 1899 the nervous symptoms were about as follows:

January 21, 1899. Dr. Posey reports: "Optic nerves are still paler than normal, but do not show any actual diseased condition. Right pupil, 3 mm. in size; left, 2½ mm., and the irides respond equally and freely to accommodation stimuli. With her glasses her vision is normal in both eyes; the report of her ocular condition is therefore negative, with the exception of the pallor of the discs."

February 3*d*. Pupils react equally and freely to light and accommodation. There seems to be a very slight paresis of the right side of the face. The tongue is protruded in the median line. Distinct nystagmus upon external rotation of the eyebrows. Slight ataxia in the arms. Right arm, bicipital reflex +; tricipital reflex +; muscular irritability; periosteal reflex diminished; persistent hypothenar reflex. Bicipital and tricipital reflexes increased on left arm. Slight transient hypothenar reflex in left hand. Periosteal reflexes absent. Muscular irritability in the right side of the face (Chvostek's sign). No chin-jerk. Apparent diminution of tactile sensation on right side. No diminution of pain sense. Slight diminution in tactile sense on the palm of the right hand. Patellar reflex absent even when reinforced. No Achilles tendon reflex. Inco-ordination of both legs. Station, with eyes open, slightly impaired; with eyes closed, very poor. Gait, slightly ataxic; with eyes closed, exceedingly ataxic. The hands are numb; numbness in feet, with cotton sensation. Stereognostic sensation

perfect. Occipital headache, occasionally passing to the front part of the head. No supraorbital or bulbar pain in the head. There is an indication of girdle sensation, which is apparently relieved by loosening the garments. There are frequent attacks of nausea, which is present in the night-time as well as during the day, and is relieved by eating. There appears to be slight weakness of the sphincter vesicæ. The patient has frequent attacks of vertigo, coming on suddenly and passing away in a short time, which compels her to sit down. She frequently has burning of the tongue and nose, and has had frequent attacks of severe diarrhea. There is a chronic ulcer of the nasal septum. Weight, 127½ pounds.

April 24th. Dizziness; light head; frequent micturition. Toward morning (4 A.M.) wakens with pain and discomfort in stomach from flatulence. Moving about relieves the flatus. Bowels more regular; mucus in passage of formed stools. Oil enemata have relieved the constipation. The tongue burns, and has red points of pain and abrasions of mucous membrane. Has only had one attack of colic in seven weeks.

April 27, 1901. Usual symptoms. General loss of flesh. Inability to walk increased. One finger very ataxic. Dizziness. Menses ceased in December. Sleep marked. No fever. Systolic murmur at apex transmitted to axilla and pulmonary systolic murmur. No thrill. Edema of legs. Had pneumonia in December. Appetite fair. Flatulence; indigestion; constipation. Difficult vision; misty. Urine free, but not unusually so. Tongue clean; frequent glossitis. Liver and spleen not enlarged. Attacks of acute gastritis. Much oppression, but no palpitation.

The blood-picture was as follows, in two selected from the many examinations:

February 2, 1899. Hemoglobin, 50 per cent.; red blood-corpuscles, 1,860,000; poikilocytes and white blood-corpuscles, 2000; polymorphonuclears, 72 per cent.; small mononuclears, 17 per cent.; transitional, ½ per cent.; eosinophiles, 2 per cent.; large mononuclears, 8½ per cent.

April 27, 1901. Hemoglobin, 50 per cent.; red blood-corpuscles, 1,500,000; white blood-corpuscles, 500. Differential count: Polymorphonuclears, 81⅓ per cent.; small mononuclears, 16⅓ per cent.; large mononuclears, ⅔ per cent.; transitional, ⅓ per cent.; eosinophiles, 1 per cent.; myelocytes, ⅓ per cent.

Very marked poikilocytosis. Numerous megalocytes and microcytes. Color index high. One normoblast, one typical megaloblast, and three intermediate forms found. The high color index, absence of normoblasts, the numerous megalocytes, and the leukopenia are indicative of a pernicious anemia. The rather high percentage of polymorphonuclear cells is usually more noticeable in secondary anemia.

It is of interest in the study of pernicious anemia to consider some of the diagnoses made before the patients come to us, and in looking over a series of cases that I have had recently, I find that a large majority are sent as carcinoma of the stomach, or chronic gastritis, or phthisis, or spinal-cord disease. One was called cirrhosis of the liver, and others have been sent with the diag-

nosis of Bright's disease, of valvular heart disease, and of malignant endocarditis. If an examination of the blood is not made, and we consider the fever, the heart murmurs, and the occurrences of subcutaneous hemorrhages, it is not surprising that a malignant endocarditis is suggested.

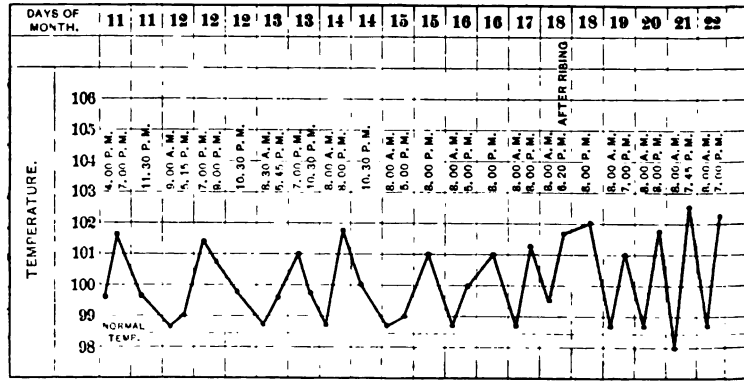
The following was supposed to be a case of cancer of the stomach. The blood-picture alone is given:

Mrs. E. Blood: *May* 29, 1900. Hemoglobin, 40 per cent.; red blood-corpuscles, 1,864,000; white blood-corpuscles, 4600. Differential count: Polymorphonuclears, 44 per cent.; small mononuclears, 53 per cent.; large mononuclears, 0.6 per cent.; transitional, 1 per cent.; eosinophiles, 1.3 per cent.; megaloblasts, 3 only; normoblasts, 0; myelocytes, 0; very extreme poikilocytosis. The low count, the low number of leukocytes, and the differential count favor pernicious anemia. The hemoglobin is hardly as high as is usually seen in such cases; the presence of megaloblasts and absence of normoblasts is also in favor of pernicious anemia.

The next case was thought to be malaria or endocarditis.

Mr. K. Blood: Hemoglobin, 50 per cent.; red blood-corpuscles, 2,864,000; white blood-corpuscles, 7400. No malarial parasites; no poikilocytosis. Differential count: Polymorphonuclears, 86⅔ per cent.; small mononuclears, 8⅓ per cent.; large mononuclears, 3 per cent; transitional, 1⅔ per cent.; eosinophiles, ⅓ per cent.; no nucleated red cells; 3 myelocytes; very little poikilocytosis, though cells are small.

The appended chart shows the temperature-range for about ten days.



Dr. Billings: So far as I have been able to gather from the literature on this subject, the spinal-cord changes are said to be characteristic in that, first, the nerve-roots themselves are intact, as you see in these photographs; second, that the afferent portions of the cord are first involved; third, that the efferent columns are next affected, and then the degeneration may become irregular, and the irregularity increases the higher the disease ascends. There is no shrinkage in these columns, even though they are degenerated. That is mentioned in all the reported cases.

A DEMONSTRATION OF SOME FEATURES OF PHOTO-MICROGRAPHY.

By CHARLES S. BOND, M.D.,
OF RICHMOND, IND.

Prof. D. W. Dennis, who holds the chair of Biology in Earlham College, and myself about a year ago ordered from Zeiss, Germany, the latest model of microscope for the purpose of photomicrography. The microscope is supplied with an adjustable abbé condenser, iris diaphragms, and modern sub-stage. The objectives are designed for photograph work, and include the following lenses: 2 mm., 4 mm., 8 mm., 16 mm., 35 mm., and 70 mm. The eye-pieces are also designed for such work, and are designated as the 4, 6, and 8 compensating eye-pieces, and a 4 projecting eye-piece for special work. All other parts of the instrument were purchased from Bausch & Lomb. The optic bench, which is 43 inches long by 15 inches wide, is sustained three feet from the floor by heavy iron legs, adjustable on the floor by binding screws in the feet. This bench has a track on its upper surface, on which slides the smaller secondary bench that supports the optic instruments for lighting the object. This bench also is adjusted by screws to any desired position. At the further end of this table stands an arc light of about a thousand candle-power. In front of this light is a large condenser, containing four glasses, which has a sliding adjustment to change the focal character of the light. This condenser, as well as all other parts of this bench, is mounted on a track, which binds all to the same optic axis when properly adjusted for work. In front of this condenser is a ray filter-holder, with two compartments, for properly converting the light. Next in order come an alum cell to remove the heat, a field diaphragm, a shutter to admit or obstruct light, and a double convex lens. The camera bench is supported in the same manner as the optic bench, and is 7 feet 2 inches long; the bellows slide back and forward in a grooved track at

the pleasure of the operator. The microscope stands on the end next to the optic bench and, by supports which are adjustable, is kept free from motion in other parts of this bench. These supports were designed by us, and comprise four screws, with wide base and heavy tops, placed under each corner of the microscope stand on the table, and adjusted to the optic axis of the light. The camera has a range of 75 inches from the stage to the microscope, and a working range of 50 inches. The ground-glass is 9 x 9 inches, and is interchangeable for the plate-holder. The camera is also adjustable to the axis of the light by lateral and vertical screws. A very perfect device has also been arranged by us for centering the object on the ground-glass. This consists of two pulleys, one of which is placed on each of the adjusting screws of the microscope stage. On the camera table, immediately beneath these pulleys, are to be found corresponding ones which form the terminals of two long rods running to the opposite end of the table. One of the rods is hollow and encloses the smaller. These have milled heads at their distal extremities, and can be moved at the will of the operator, either separately or combined, making either simple or compound motions of objects on the ground-glass. By this means the centering of an object, or searching the field, becomes very easy and accurate. We have also devised a rod and pulley for focusing the object on the ground-glass by means of a rapid adjustment screw. For work in low powers it has proven very serviceable and a great time-saver.

For definite work all possible adjustments of the instrument should be known and accurately recorded in tables, which should be placed in view of the operator. In order that these tables be made it is necessary to have the instrument marked in some definite manner. We have commenced at the microscope stage and marked on the table of the camera, at intervals of inches and half-inches, the distance from this point to the opposite end of this table. Again, on the optic bench, and on the rod bearing the instruments of this bench, we have placed similar markings, beginning with the stage and going in opposite directions from former markings. By means of a stage micrometer a table can be prepared of amplifications which will show the linear diameter of any object with any objectives and all eye-pieces at any distance the camera may be from the stage of the microscope. On the other hand, if a definite amplification be desired the table will show how the instrument should be set up to produce the desired result.

Again, this table will show several different adjustments for the desired diameter, and a choice can be made with reference to the effect wished to be produced in depth of focus, etc.

As the optic bench must bring the light in a straight line into the axis of the abbé and camera, and as the length of this pencil of light

Instrument for photomicrography.

differs with the different objectives, the adjustment of all these important factors must be known at all times.

The combinations which are possible with the parts of this bench are so numerous that it would not be likely that by chance the instrument could be adjusted on two occasions alike for the same objective. It is necessary, therefore, for good work, to ascertain the definite

location of every important part of this bench when the best trial result has been obtained. This can only be done by tables and markings on the optic bench as before mentioned.

We have found that three adjustments for this bench give good results in focus for all objectives. We have indicated these on our table as first, second, and third positions.

The *first* position places the light at a known point. The condenser has only one set of lenses next to the light. The double convex lens and the abbé are omitted, and the 70 mm. and the 35 mm. objectives are used.

The *second* position includes the whole of the condenser, with different position of light, and is used for middle powers.

The *third* position places the light much further away from the stage, and includes the condenser, double convex lens, and abbé, and gives good results in high-power work.

It is easy to set up these positions in a few moments when the kind of work is determined upon from such tables.

For definite work it finally becomes necessary to make a careful record of all these conditions at every exposure, together with memoranda of size of all diaphragms, number of ray filters, ground-glass, and kind of plate used, time of exposure, and kind of developer. This can be done by chart, arranged for rapidly filling in each time.

Finally, a room must have been prepared with a solid cement floor, having a tiled surface, sliding shutters in front of the windows, tight-fitting doors, and otherwise arranged in all respects for the best work in photography.

The light must be so arranged that it will pass continuously through the optic axis of all lenses from its source to the center of the ground-glass. This axis should be ascertained by small apertures made in diaphragms that should be provided for all important lenses.

As the light is a source of much variation as to intensity the timing of exposures is a guess, made more or less accurate by a careful study of the tables and lighted ground-glass. Even then a trial exposure will be made necessary on new positions often, with the same kind of plates. Other elements, such as temperature, kind of developer, and degree of development, make this rebus still more complex, so that the most exacting methods will meet with many failures.

The class of the object as to color, density, size, and structure

gives many opportunities for experiment in order to obtain the most contrast on the ground-glass, which should be free from defraction and other objectionable features.

If now we wish to expose an object, say the snail's tongue in the following plates, we place all the optic bench in the first position, and as the tongue is nine-sixteenths of an inch long, the 70 mm. lens must be used to admit it all in objective. The camera is placed as close as possible (say twenty inches) from the object. As the bellows is now extended the object soon reaches the full width of the ground-glass, and thus limits the further amplification of the object. It is now found by consulting the chart that this extension of bellows is equal to 25 diameters. From about 9 to 25 diameters, therefore, is the possible limit for this object. As the source of light is small the image of the light on the ground-glass is also small, and the illumination is very uneven over the plate. In order, therefore, to have an evenly lighted field some diffusion of light must be had. This may be accomplished in several ways, but the usual method followed by others is to insert a piece of ground-glass in the axis of light. A better way sometimes, when an abundance of light is to be had, is to cause the light to be thrown out of the optic axis, so as to obtain only reflected or refracted rays. By this method the light is much dimmed and a longer exposure is made necessary; but that is of little consequence, as the time is not unduly long. As the objective has a large aperture and only slightly convex, the rays of light fall practically in the same focus over the whole of the ground-glass, and, therefore, no difficulty is experienced either in focus or diffraction. As the light is but little diffused, any well-stained object will appear in good contrast on the ground-glass, so that a ray-filter for color conversion is generally unnecessary. The diaphragms must be almost at maximum size, since otherwise the object will be encroached upon.

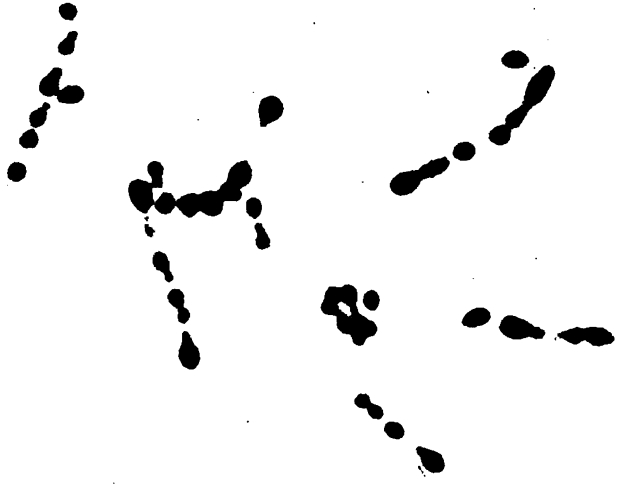
In case of the second position many of these conditions are altered. For example, the 16 mm. lens will be used. Our tables show that this lens, together with the eye-pieces and use of the extension bellows, has amplification power of from 100 to 675 diameters. The crystalline lens of the fetus of a chick,[1] in the appended views, will serve as

[1] On account of expense of reproduction only ten photomicrographs are shown out of the thirty-five demonstrated at the meeting in Washington, which accounts for omissions referred to in the text.

an example of this class. The light remains in the same position as in the first example, but the whole of the large condenser is in place, while the abbé and double convex lens are still omitted. The projection eye-piece is used and the camera is drawn back to twenty-five inches from the object. At this point the object is enlarged sufficiently for all purposes, and the field is evenly lighted if the light be properly adjusted. If the light be uniform over the plate, but slightly too high or too low or too far to either side, a line of diffraction will be seen on the opposite side from the strained position of the light, and the light must be readjusted. Stopping the light down too much by the bed diaphragm will also occasion an unequal distribution of light about the object in the way of diffraction lines on all sides. On the other hand, too much light will dim the view of the object to such an extent that it may be entirely lost. The proper experience with this diaphragm, therefore, becomes of great value, and must be noted when once obtained for definite work. Good photomicrographs can be made with this object and combination named without the use of the ground-glass on the optic bench. For the best work without such ground-glass the light should be centered perfectly, and its amount should be controlled by the asbestos diaphragms placed in the end of the large condenser next to the source of light. If the light be unequal over the surface of the ground-glass in the camera, the abbé may be placed in position, and then be drawn backward from the object until the light becomes even. This plan admits more light than the ground-glass, and succeeds equally well.

In the third position the light is placed eight and one-fourth inches nearer the object than in former positions. The condenser is also moved forward, and the double convex lens and abbé are added to the optic bench. The asbestos diaphragms are removed in front of the light, while the field and abbé diaphragms are opened to their full extent if the ground-glass is to be inserted in the axis of the light. If the ground-glass is to be omitted the field diaphragm must be small, and even then for objects with great contrast and sharp outlines diffraction will appear in the negative. The two diphtheria slides in appended views will serve as examples of this class of high-power work. The smallest view has an amplification of 2000 diameters, while the second has been magnified 3000 diameters and the third 4000 diameters. It will be seen that the first has the most definition, while

Diphtheria B. D. 2000.

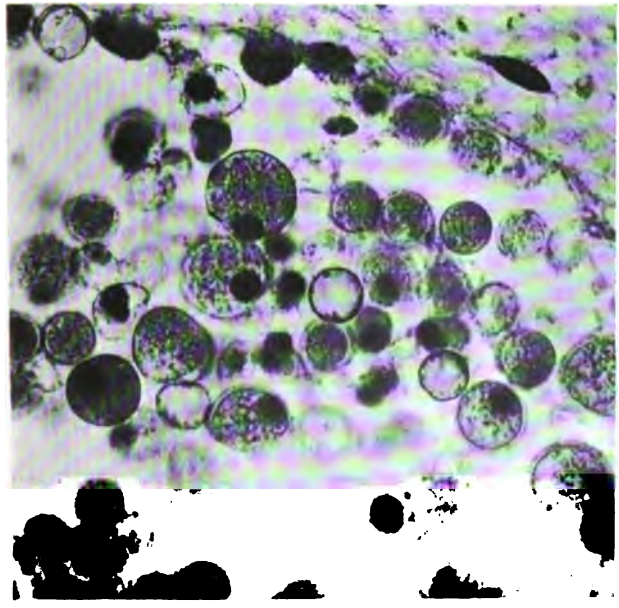


Diphtheria B D. 4000.

Sarcina. D. 3000.

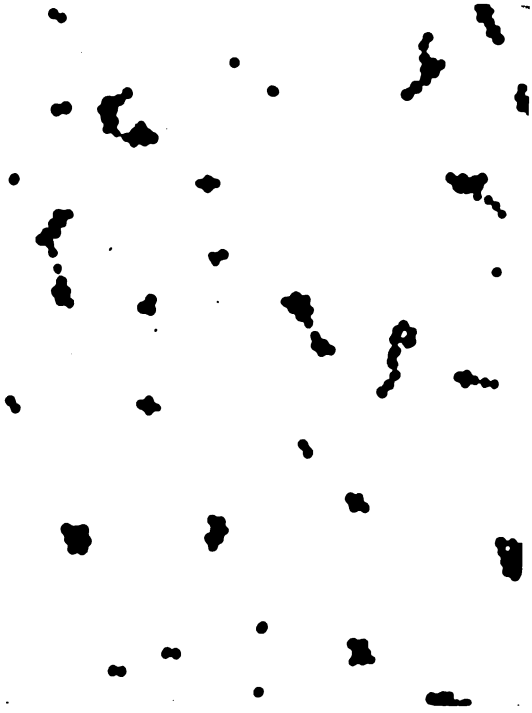
Communis Coli, B. D. 3000.

Anthrax B. D 3000.



Fœtal blood. D. 2000.

Malignant œdema.
D. 3000.



Erysipelas B D. 2000.

Snail's tongue. D. 10.

the greater ones have differentiation at the expense of sharpness. It must be determined, therefore, which feature is to be shown in making choice of these powers. It is with this high-power work that a limitation is placed on the field yielding a distinct image and uniform focus, even with very thin objects in one plane. The best lens is so far unable to maintain a perfectly flat field, under the most favorable conditions, of more than three or four inches in diameter with the highest power work. The depth of focus is shallow, but most remarkable with the latest Zeiss lenses, as may be seen in many of the following views in this class of work.

In conclusion, I wish to say that it is my belief that the time has come when photomicrography is to take the place of much of the work now done from the camera lucida and extemporized microscopic fields, and that we shall learn more from the faults in such views than from preconceived notions injected into them through idealized work.

THE ETIOLOGY OF ACUTE HEMORRHAGIC PANCREATITIS.

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(*From the Pathologic Laboratory of the Johns Hopkins University and Hospital.*)

Pathologic Report.

In many reported cases of hemorrhagic and of gangrenous pancreatitis symptoms of cholelithiasis have been associated with the fatal illness, and at autopsy calculi have been found in the gall-bladder or in the bile passages. In a recent article[1] I collected from the literature thirty-one cases of this character and described an additional instance. In eight of these cases, including the one which I reported, a gall-stone was found at autopsy lodged near the orifice of the common bile-duct, or there was evidence that one had shortly before death occupied this position. Since the common bile-duct and the duct of Wirsung unite in the diverticulum of Vater before they enter the intestine, a calculus so located might occlude both ducts. Though in the greater number of these collected cases calculi were found at autopsy, none was situated near the junction of the two ducts. Nevertheless, since, as was pointed out, death with intensely hemorrhagic inflammation of the gland has in several instances followed within forty-eight hours the onset of symptoms, and a calculus has been found near the duodenal orifice of the common duct, it is readily conceivable that a stone temporarily lodged in the position indicated might produce grave alteration of the gland before its final expulsion into the duodenum. In seven of the thirty-one cases death followed the onset of symptoms, intense abdominal pain, vomiting, and profound collapse

[1] Opie. American Journal of the Medical Sciences, 1901, vol. cxxi. p. 27.

within forty-eight hours, and at autopsy the pancreas was the seat of hemorrhagic infiltration. In seventeen instances in which the fatal illness was of longer duration, seven days to four months, the pancreas was gangrenous, and there was often evidence of previous hemorrhage. There can be little doubt that gangrenous pancreatitis is a late stage of the hemorrhagic lesion.

That acute pancreatic disease is frequently associated with cholelithiasis has been confirmed by cases reported since the preparation of the article referred to. The two conditions were present in three cases recently described by Lund,[1] in two by Bryant,[2] and in one by Stockton and Williams,[3] by Struppler[4] and by Hahn.[5] The relative frequency with which acute pancreatitis is accompanied by cholelithiasis is difficult to estimate. In some cases the lesion has been diagnosed on the operating-table, and, no autopsy being obtained, the condition of the bile passages has not been determined. In a very large proportion of the cases the autopsy report is so meagre that the presence or absence of gallstones is not evident. Lund records the relatively large number of six cases of acute pancreatitis, one suppurative, five hemorrhagic or hemorrhagic and gangrenous. Two of the five cases he describes as hemorrhagic peripancreatitis. In three of these five cases the gall-bladder or the bile passages contained small calculi in large numbers, while in the remaining two no autopsy was obtained. In the two cases reported by Bryant hemorrhagic pancreatitis was associated with gallstones. In only one of the five cases of Hahn were gallstones present, but in one of his cases hemorrhagic infiltration of the gland followed a pistol-shot wound, and in another recovery followed operation. Gallstones were, therefore, present in six of eight cases described with autopsy by the three writers who have recently reported more than one instance of the disease.

In view of the fact that in several instances a calculus has been found at autopsy so lodged as to occlude the pancreatic duct, there can be no doubt that the frequent association of the two conditions is the result of an etiologic relationship. The common bile-duct and the larger pancreatic duct lie side by side as they penetrate the wall

[1] Lund. Boston Medical and Surgical Journal, 1900, vol. cxliii. p. 543.
[2] Bryant. Lancet, 1900, vol. ii. p. 1341.
[3] Stockton and Williams. Philadelphia Medical Journal, 1900, vol. vi. p. 649.
[4] Struppler. Deutsch Arch. f. klin. Med., 1900, vol. lxix. p. 206.
[5] Hahn. Deutsch Zeitsch. f. Chir., 1900, vol. lviii. p. 1.

of the duodenum, and are often separated near their junction only by a thin membranous septum. Before entering the duodenum at the summit of the bile papilla they unite to form a short channel—the diverticulum of Vater. From a study of the case previously reported it seemed not improbable that a calculus lodged in the common bile-duct near the termination might cause partial occlusion of the pancreatic duct and subsequent changes in the pancreas as the result, possibly, of bacterial invasion. This case, as well as those recorded in the literature, afforded, however, no explanation of the pathogenesis of the hemorrhagic inflammation. At the autopsy recently performed upon a case whose clinical history has been described by Dr. Halsted[1] I was able to demonstrate the mechanism by which this lesion was produced.

Autopsy. The body, which is still warm, is that of a large man with very abundant subcutaneous fat. The skin has a bluish, cyanotic appearance. Passing downward from the right costal margin to a point 10 cm. from the symphysis pubis is a longitudinal incision, closed in great part by subcutaneous silver-wire sutures. Crossing the epigastric region and meeting the first at right angles is a second incision. At their angle of junction the wound is unclosed for a short distance, and gauze packed about by rubber protective passes into the abdominal cavity.

The peritoneal cavity contains a moderate excess of bloodstained serous fluid. The general peritoneal surface is smooth. Fat is present in very great amount in the omentum, in front of the peritoneum of the anterior abdominal wall below the umbilicus, in the mesentery, in the retroperitoneal tissue, and as appendices epiploicæ upon the surface of the large intestine. Studding the fat in the various situations named, and conspicuous upon its translucent surface, are small, usually round opaque white areas 2 or 3 mm. in diameter, often surrounded by a narrow zone of injection. They are superficially situated and extend usually less than 1 mm. below the surface. They are most abundant in the omentum and in the retroperitoneal fat adjacent to the pancreas. The gauze drain previously mentioned passes between the stomach and the transverse colon and lies in contact with the retroperitoneal fat immediately below the head of the pancreas. Here the tissue has a reddish-black discoloration.

[1] Johns Hopkins Bulletin, 1901, vol. xii. p. 179.

The pancreas is represented by a blackish, swollen mass extending from the descending part of the duodenum to the spleen. The fat in contact with its splenic end has a similar blackish color and is soft and friable. The pancreas is greatly increased in size, is irregularly cylindric in shape, and measures 5.2 cm. anteroposteriorly, 5.5 cm. from above down, and 16 cm. in length. The anterior surface is smooth and has an almost uniform black color in places with a reddish tint. On section, the gland substance is found to be in great part transformed into black and reddish-black material. The head of the organ for a distance of 2.5 cm. from the duodenum is firm, grayish-yellow, with well-marked lobulation, and has the appearance of fresh normal pancreas. The tissue which is in immediate contact with this well-preserved gland substance is soft and black in color, mottled here and there with small areas of dull red; gland lobulation is still very obscurely marked. The distal half of the organ shows a similar mottling of black and reddish areas, with in places small islands of yellowish, relatively preserved tissue. The largest of these, which is of reddish-yellow color gradually passing into the surrounding reddish-black, is 1.5 cm. in diameter and is situated near the middle of the body. At the splenic extremity is a slightly smaller mass of intact gland substance. On opening the splenic vein where it lies in contact with the pancreas the intima is found to have a mottled yellow, black, and red appearance, due to changes in the underlying tissue. Occupying a portion of the lumen is a mixed red and yellow thrombus mass, firm in consistence and adherent to the intima.

The duodenum was opened and the common orifice of the bile and pancreatic ducts examined. The papilla is prominent, but its orifice is of small size, measuring about 1 mm. in diameter. The common bile-duct, which near its termination is completely embedded in the substance of the pancreas, is slightly distended. By very firm pressure on the gall-bladder several drops of bile can be squeezed, with difficulty, into the duodenum. The gall-bladder when opened is found to contain a moderate amount of viscid, blackish bile; no concretions are present. The termination of the pancreatic duct, which is surrounded by the well-preserved pancreatic substances in contact with the duodenum, was exposed by dissection and found to unite with the common bile-duct 10 mm. from the summit of the bile papilla. A probe passed down the common duct was stopped 4 mm. from the latter point, and

it was not possible to touch it with a second probe passed into the narrow orifice. Careful examination disclosed a small grayish-white, very firm concretion 3 mm. in diameter, snugly filling the diverticulum of Vater, from which it could not escape through the narrow duodenal orifice. The pancreatic duct where it passes through the intact tissue of the head is, like the common duct, stained bright green with bile.

The heart and lungs are apparently normal. The liver weighs 1350 grams. The surface is smooth and of yellowish color; upon the upper surface of the right lobe are conspicuous slightly depressed dull red areas which are irregular in shape, the larger about 2.5 cm. across. The cut surface of the organ has a bright yellow color, the periphery of the lobulus being golden-yellow, the central part reddish. Corresponding to the superficial red areas, the liver substance has a similar dull red appearance, the periphery of the lobulus being marked by narrow yellow zones. Such altered tissue has at times an irregular wedge-shaped outline, and within it are found portal veins distended and plugged with red thrombus material. Following the vein in one of these areas toward the portal trunk the thrombus stops abruptly, and near its end is of yellowish-white color, representing, probably, embolic material from the thrombosed splenic vein. The spleen is not enlarged and weighs 140 grams. The organ is flaccid, but fairly firm in consistence.

The stomach contains a small amount of blackish, semi-fluid material. The duodenum and remainder of the small intestine contains similar material. The kidneys, weighing together 290 grams, appear to be normal, except for the presence of opaque yellow striations near the apices of the pyramids. The adrenals, the bladder, the seminal vesicles, and the prostate are normal. Upon the intima of the aorta are a few slightly raised opaque yellow patches of small size. The urine contained in the bladder does not reduce Fehling's solution.

Microscopic Examination of the Pancreas. A section passing through the line of demarcation between the intact parenchyma in the head of the gland and the adjacent necrotic tissue shows a very abrupt transition from one to the other. On the one side the pancreatic tissue is well preserved, the secreting cells are normal in appearance and their basal zone stains deeply with hematoxylin, while the islands of Langerhans are fairly abundant and appear to be

normal. The loose interlobular areolar tissue is everywhere infiltrated with red blood-corpuscles; polynuclear leukocytes are present in large number and often form collections of considerable extent. Eosinophilic leukocytes are numerous and fibrin is abundant. Between the acini are a few polynuclear leukocytes. Within the margin of the intact tissue are several small areas where the parenchyma is undergoing necrosis. The secreting cells no longer stain with hematoxylin, but assume a homogeneous clear pink color with eosin; the nuclei which are still preserved are much smaller than those of the normal cells and, unlike the latter, are irregular and distorted and stain homogeneously. Small hemorrhages have taken place into the interacinar tissue of such an area, and polynuclear leukocytes are present in moderate number. Near by, in similarly localized areas, the process is more advanced, and the parenchymatous cells are replaced by formless material which, staining faintly, is mingled with a few nuclear fragments and is densely infiltrated with polynuclear leukocytes and red blood-corpuscles.

The transition from relatively normal parenchyma containing a few islands of necrosis to wholly necrotic tissue is very abrupt and is marked by a zone composed of nuclear fragments, polynuclear leukocytes, red blood-corpuscles, and fibrin. That part of the section which corresponds to the black and reddish-black material seen macroscopically is necrotic, nuclei are no longer present, and though the architecture of the gland is obscurely definable, both parenchyma and connective tissue stain only with eosin. At intervals in areas of varying extent the tissue has a dark-brown discoloration due to the presence of brown pigmented material which appears to be changed blood.

Sections from the body and tail of the organ present the appearance described above. In the intact tissue of the tail well-preserved islands of Langerhans are particularly numerous. In a section from the body nuclei still persist immediately about an artery, though the surrounding tissue is universally necrotic. Its endothelial cells are swollen and in places are almost cubical. In the media and adventitia, of which the vasa vasorum are preserved, polynuclear leukocytes are very numerous.

In sections stained by Weigert's method for the demonstration of fibrin was noted a histologic detail inconspicuous by other methods.

Capillary vessels in the living tissue near the margin of necrosis, as well as in the immediately adjacent necrotic part, have undergone hyaline thrombosis, and form conspicuous deep blue and often branched lines, as though injected. Examination with high magnification demonstrates at times a close meshwork of fibrils in these vessels. In sections stained with hematoxylin and eosin their contents take a homogeneous bright pinkish-red stain, and red blood-corpuscles are no longer seen, as in adjacent capillaries.

In sections stained for bacteria with methylene-blue, gentian-violet, and by Weigert's method none was discovered.

Bateriologic Examination. Plate cultures in agar-agar were made at autopsy from the heart's blood, peritoneal cavity, pancreas (aërobic and anaërobic on hydrocele agar-agar), gall-bladder, liver, spleen, and kidney. They were studied by Mr. V. H. Bassett, to whom I am indebted for the following report: Cultures from the heart's blood, spleen, and gall-bladder gave negative result. The anaërobic culture from the pancreas showed no growth after an incubation of seventy-two hours. The aërobic agar-agar plate from the pancreas contained at the end of twenty-four hours a single superficial colony of a pigment-forming coccus whose cultural characters indicated that it was a contamination from the air. The streptococcus pyogenes and the staphylococcus epidermidis albus were isolated from the peritoneal cavity. The colon bacillus was present in cultures from the liver and kidney.

Anatomic Diagnosis. Cholelithiasis; calculus impacted in the diverticulum of Vater, partially filling it and occluding its duodenal orifice. Acute hemorrhagic pancreatitis; disseminated abdominal fat necrosis. Partial thrombosis of the splenic vein; embolism and thrombosis of branches of the portal vein.

The preceding autopsy has disclosed a condition which explains, I believe, the pathogenesis of those cases of acute hemorrhagic and gangrenous pancreatitis which are associated with gallstones. The diverticulum of Vater was 10 mm. in length. Lodged at its apex, blocking its duodenal orifice, was a small calculus only 3 mm. in diameter, but too small to pass the narrow opening. Though it occluded the duodenal orifice of the diverticulum it was so small that the orifices of the common bile-duct and pancreatic duct were unobstructed. The

two ducts were, therefore, converted into a continuous closed channel from which it was not possible for either bile or pancreatic juice to escape.

On dissecting the pancreatic duct where it passed through the unchanged parenchyma in contact with the duodenum it was found, like the bile-duct, to be stained bright green with bile. Where, as in this case, the two ducts become a closed channel, the entrance of bile into the pancreas or of pancreatic juice into the bile passages would depend upon the relative pressure in the two ducts. The pressure at which bile and pancreatic juice are secreted being small, any slight difference that might exist would be overcome by the gall-bladder, a muscular organ which at intervals forces bile in considerable quantity along the common duct.

A small calculus only partially filling the ampulla of Vater can convert the two ducts into a continuous channel, while a larger stone might simultaneously obstruct the duodenal orifice of the diverticulum and the orifices of the two ducts which enter it, thus damming back bile and pancreatic juice upon their respective glands. In the present case, as previously mentioned, the diverticulum measured 10 mm. in length, the calculus 3 mm. in diameter. In many cases of hemorrhagic and gangrenous pancreatitis gallstones found in the gall-bladder and bile passages at autopsy have been small and are often described as pea-sized. This statement is made in the reports of Day,[1] Cutler,[2] Kennan,[3] Simpson,[4] Chiari[5] (two cases), Smith,[6] Ehrich,[7] Fränkel,[8] Körte,[9] Morian,[10] Rolleston,[11] Grawitz,[12] Opie,[13] Bryant,[14] and Lund[15] (three cases).

Anatomic peculiarities of the diverticulum of Vater might favor or prevent the conversion of the two ducts into a closed channel. The

[1] Day. Boston Medical and Surgical Journal, 1892, vol. cxxvii. p. 569.
[2] Cutler. Ibid., 1895, vol. cxxxii. p. 354.
[3] Kennan. British Medical Journal, 1896, vol. ii. p. 1442.
[4] Simpson. Edinburgh Medical Journal, 1897, vol. ii. p. 245.
[5] Chiari. Wiener med. Wochensch., 1876, vol. xxvi. p. 291; ibid., 1880, vol. xxx. pp. 139, 164.
[6] Smith. British Medical Journal, 1897, vol. ii. p. 468.
[7] Ehrich. Beiträge z. klin. Chir., 1898, vol. xx. p. 316.
[8] Fränkel. Münch. med. Wochensch., 1896, vol. xliii. pp. 813, 844.
[9] Körte. Arch. f. klin. Chir., 1894, vol. xlviii. p. 721.
[10] Morian. Münch. med. Wochensch., 1899, vol. lxvi. p. 348.
[11] Rolleston. Transactions of Pathological Society of London, 1893, vol. xliv. p. 71.
[12] Grawitz. Münch. med. Wochensch., 1899, vol. xlvii. p. 813.
[13] Loc. cit. [14] Loc. cit. [15] Loc. cit.

description of the ampulla given by Sappey,[1] Testut,[2] Henle,[3] and Quain[4] does not differ materially. It may be described as a somewhat conic cavity into whose base open the two ducts; the apex situated at the summit of the diverticulum of Vater is their common duodenal orifice. Its length varies from 6 to 7 mm. according to Testut, from 7 to 8 mm. according to Sappey. Occasionally the two ducts have no common channel, but open by separate orifices upon the summit of the bile papilla. Claude Bernard[5] described a variety of termination which has since been observed by anatomists. The bile-duct is prolonged as far as the mucosa of the duodenum, upon which it opens by a circular orifice. The terminal part of the pancreatic duct embraces the bile-duct like a gutter, and its orifice has the outline of a crescent. Where the ampulla is very short or the two ducts open separately into the duodenum it is evident that an impacted calculus could not render continuous the lumina of the two ducts.

I have recently examined the diverticulum of Vater in a small number of cases available for study. In three specimens (Nos, 3, 11, and 13) the ducts opened into the intestine by separate orifices. The following figures represent the length of the ampulla in these cases:

No. 1	5 mm.	No. 11	0 mm.
" 2	6 "	" 12	6.5 "
" 3	0 "	" 13	0 "
" 4	4 "	" 14	5.5 "
" 5	5 "	" 15	1.5 "
" 6	7 "	" 16	1 "
" 7	10 "	" 17	11 "
" 8	7 "	" 18	6 "
" 9	5.5 "	" 19	2.5 "
" 10	2.5 "	" 20	6 "

No. 6 is from the case previously reported, No. 7 is that described in the present article. The figures are cited to show that the length of the so-called diverticulum varies considerably.

Another anatomic factor of considerable importance is the size of the duodenal orifice of the ampulla. Hyrtl[6] states that this opening is narrower than the lumen of the gall-duct at any point, or is at least less distensible, so that gallstones often remain here impacted.

[1] Sappey. Traité d'anatomie descriptive, Paris, 1889.
[2] Testut. Traité d'anatomie humaine, Paris, 1894.
[3] Henle. Handbuch du Systematischen Anatomie des Menschen, Braunschweig, 1873.
[4] Quain. Elements of Anatomy, London, 1896.
[5] Quoted by Sappey.
[6] Hyrtl. Handbuch der topographischen Anatomie, Wien, 1882.

In the autopsy described the opening measured only 1 mm. in diameter. It is usually 2 to 2.5 mm. in diameter; in one specimen (No. 9) it measured 4 mm. across.

Experimental Study.

Hemorrhagic pancreatitis has been produced experimentally by the injection of a variety of irritating substances into the pancreas, but no attempt has been made to reproduce the lesion by the use of bile.

Thiroloix[1] injected several drops of deliquescent zinc chlorid into the duct of Wirsung in a dog. Death occurred suddenly, after a short interval, and the pancreas was represented by what appeared to be a blackish clot. Hlava[2] injected artificial gastric juice into the pancreatic duct. The fluid, containing hydrochloric acid in the proportion of 1 to 1000, caused death in three days; the pancreas was hyperemic, and in the fat of the omentum and of the mesentery were numerous foci of necrosis. Death on the tenth day followed the injection of 5 c.c. of artificial gastric juice with hydrochloric acid, 4 to 1000; the pancreas was the seat of hemorrhagic infiltration, and the omentum and mesentery contained foci of fat necrosis. He suggests that in human cases hyperacid gastric juice may be forced by antiperistaltic action of the intestine into the pancreatic duct, thus causing the condition. Hlava has produced a hemorrhagic lesion of the gland by injecting cultures of the bacillus coli communis, bacillus lactis aerogenes, and bacillus capsulatus of Friedländer, but thinks that the change is the result of the acid products of these organisms.

Oser[3] records the injection of 4 c.c. of $\frac{1}{40}$ normal sulphuric acid solution into the pancreatic duct of a dog. Death followed in twenty hours. In the duodenal part of the gland was a hemorrhagic area the size of a pea, where the tissue was destroyed and the structure no longer recognizable. By the injection of the ferment, papain (0.2 grams in 30 c.c. of water), into the duct of a dog, Carnot[4] caused the death of the animal in twenty-five hours; the pancreas was everywhere infiltrated with blood, but there was no necrosis of fat. Smaller

[1] Thiroloix. Quoted by Carnot (see below).
[2] Hlava. Quoted by Flexner (see below).
[3] Oser. Die Erkrankungen des Pankreas. Nothnagel's Spec. Path. u. Ther., Wien, 1898, vol. xviii. ii. p. 286.
[4] Carnot. Paris Thèsis, 1898.

doses did not produce hemorrhagic lesions. The same writer produced hemorrhagic pancreatitis by the injection of the diphtheria toxin into the pancreatic duct of a rabbit. A suspension of the bacillus coli communis (12 c.c.) caused a similar lesion, fatal in twenty-four hours. Subsequent injections of the same organism caused inflammatory changes without hemorrhage.

More varied and successful experiments have been performed by Dr. Flexner[1] in this laboratory. In ten experiments performed upon dogs hydrochloric acid, varying in strength in different instances from 0.5 per cent. to 2 per cent., and in amount from 3 to 8 c.c., was injected into the pancreatic duct of dogs. In six instances there resulted hemorrhagic inflammation of the gland, accompanied in five by focal fat necrosis. In three of these six cases death followed the operation within twenty-four hours; in two the animals were killed. In the remaining experiments purulent or chronic interstitial inflammation resulted. Hemorrhagic lesions were produced in two dogs by the use of nitric acid (4 c.c. of a 2 per cent. solution and 5 c.c. of a 1 per cent. solution); in one by the use of chromic acid (8 c.c. of a 1 per cent. solution). In a second series of experiments sodium hydroxid solution (2.5 to 5 c.c. of solutions varying in strength from 1 per cent. to 2 per cent.) was employed. Hemorrhagic lesions resulted in three cases, and were accompanied by fat necrosis in at least two. Suspensions of bacteria were used in a third series. Hemorrhagic inflammation was caused by the bacillus pyocyaneus and in the three experiments by the bacillus diphtheriæ, but was unaccompanied by definite fat necrosis. In two experiments the lesion followed the injection of 5 c.c. of a 2 per. cent. solution of formalin into the duct and was associated with fat necrosis.

The experiments cited show that a variety of substances injected into the duct of the pancreas cause hemorrhagic inflammation. How far they can be used to explain the pathogenesis of human cases is doubtful. The suggestion of Hlava that gastric juice may be driven by antiperistaltic action of the intestine into the ducts is not supported by any evidence. The relation of hemorrhagic pancreatitis to bacterial invasion from the intestine has not been demonstrated. The condition observed in the autopsy described has suggested a mechan-

[1] Flexner. Contributions to the Science of Medicine. Dedicated to Wm. H. Welch, M.D., Baltimore, 1900, p. 743.

ism by which an irritating substance can make its way into the organ. Can the hemorrhagic inflammation observed in human cases and produced in animals by means of various irritants be reproduced by the injection of bile into the pancreatic duct?

In the following experiments the duodenum was opened for a distance of several centimeters opposite the larger pancreatic duct. The blunt-pointed nozzle of a syringe was inserted into the orifice of the duct, and bile obtained from the same or from a second dog was injected into the organ. The operations were performed with the usual antiseptic precautions, and the duodenal wound was closed by submucous mattress sutures. I desire to express my thanks to Mr. Bassett, Mr. Haskell, and Mr. W. Marshall for assistance in the performance of these operations.

EXPERIMENT I. Into the larger pancreatic duct was injected 5 c.c. of bile obtained from a second dog. The animal was killed seven days later. The peritoneal cavity contains a small amount of bloody fluid, and the surface is injected. The large and several loops of the small intestine are firmly adherent to the splenic arm of the pancreas, and on separating them are exposed pockets containing very thick viscid fluid of dull red color. The walls of these pockets have in places the opaque white appearance of necrotic fat. The splenic part of the gland and the duodenal part, above the duodenal orifice of the main duct, is very firm in consistence, and both upon the surface and on section shows a mottling of opaque yellowish-white areas separated by deep hemorrhagic red. Over a considerable area at the junction of the duodenal and splenic parts of the gland the tissue is almost uniformly grayish-yellow, and is in places softened and disintegrated. Cultures and cover-slips from the peritoneal cavity and from the substance of the pancreas contained no bacteria. Microscopic examination of the splenic and duodenal parts of the gland show that wide areas of parenchyma, including entire groups of lobules, are necrotic and the secreting cells, which have a homogeneous hyaline appearance and are stained deeply with eosin, contain no nuclei. At the margin of such areas red blood-corpuscles and polynuclear leukocytes are present in great number, and fibrin is abundant. In places the bodies of the secreting cells have been converted into formless detritus mingled with red blood-corpuscles and leukocytes. The interstitial tissue may be implicated in the general necrosis, but often it has undergone very active proliferation and has in small part replaced the disintegrated acini. Islands of parenchyma still persist in places and are surrounded by newly-formed fibrous tissue containing red blood-corpuscles and polynuclear leukocytes.

EXPERIMENT II. Bile (5 c.c.) from a second dog was injected as before. The animal was killed at the end of five days. Lightly adherent to the part of the pancreas which is in contact with the duodenum are several loops of

small intestine. In the omental fat are several opaque white areas of fat necrosis, while near the splenic extremity are several inconspicuous foci of similar nature. In the duodenal part of the gland in the neighborhood of the orifice of the larger duct for a distance of 3.5 cm. there is extensive hemorrhagic infiltration separating islands of parenchyma. In places the gland substance is soft and of gray necrotic appearance. The splenic part is firm in consistence, and at several points are areas of hemorrhagic infiltration. Microscopic examination of sections from the hemorrhagic duodenal part show wide areas of necrosis implicating both lobular and interstitial tissue. The parenchymatous cells are hyaline and without nuclei. Copious hemorrhage has taken place into these areas, and at the margin of intact tissue polynuclear leukocytes are numerous. Fibrin is abundant in the necrotic interlobular tissue. Where wide-spread destruction has not occurred there has been active proliferation of interstitial tissue, replacing in part destroyed parenchyma and containing numerous red blood-corpuscles and polynuclear leukocytes. The remaining acini are often separated by newly-formed interstitial tissue, and there is the appearance of advanced chronic inflammation. In the splenic part of the gland foci of necrosis with hemorrhage occur, and in small scattered areas there is newly-formed connective tissue.

EXPERIMENT III. After opening the duodenum 5 c.c. of bile obtained from a second dog was injected into the pancreatic duct. Death followed within twenty hours. The peritoneal cavity contains several cubic centimeters of bloody fluid, and the peritoneal surface has an irregularly distributed deep red injection. The entire omentum is studded with conspicuous opaque white areas of fat necrosis, usually round, 1 to 1.5 mm. in diameter, and surrounded by a zone of injection. They are most abundant in the neighborhood of the spleen, where superficially and on section they occupy about one-half the exposed surface. In the mesentery of the duodenum near the pancreas they are numerous, but in the remainder of the mesentery of both large and small intestine they are sparsely scattered. Similar foci are present in the retroperitoneal fat and in the properitoneal fat below the diaphragm. The splenic arm and the upper half of the attached duodenal part of the pancreas are swollen and edematous in appearance, and the lobulations are separated by tissue infiltrated with blood. The cut surface has a mottled dull red and gray color, the interstitial tissue being hemorrhagic, while minute hemorrhages are in places seen within the lobular substance. The left lung is the seat of a mucopurulent bronchitis. A culture made from the peritoneal cavity remained sterile. A short bacillus was grown from the pancreas. Microscopic examination shows that the dull red areas of the pancreas represent foci of necrosis where the parenchymatous cells stain only with eosin and no longer contain nuclei. The bloodvessels here are widely dilated, and abundant hemorrhage has frequently taken place. Polynuclear leukocytes are present, but are not very numerous. Such an area of necrosis and hemorrhage is at times limited to the central part of a lobule group, while the acini furthest from the central duct are intact. The interstitial

tissue, particularly of the duodenal part of the gland, has an edematous appearance and contains red blood-corpuscles, polynuclear leukocytes, and fibrin.

EXPERIMENT IV. By means of a sharp-pointed needle 3 c.c. of bile was withdrawn from the gall-bladder and injected into the larger pancreatic duct. The animal was killed at the end of seven days. Upon the surface of the pancreas where it is in contact with the duodenum are a few sparsely scattered opaque white areas of small size. In the omentum near the gland are a few similar foci of necrosis. The pancreas is normal in consistence, and no change is noted macroscopically. Microscopic examination shows the interstitial tissue of the splenic and duodenal parts of the gland moderately infiltrated in places with blood-corpuscles, while here and there it is distended and has an edematous appearance. The parenchyma is normal in the sections examined.

EXPERIMENT V. The operation previously described was repeated, and 2.5 c.c. of bile was withdrawn from the gall-bladder and, after opening the duodenum, injected into the larger pancreatic duct. The dog was killed at the end of four days. The pancreas, which is not adherent to the adjacent structures, is firm in consistence and has throughout a reddish-gray color, but is nowhere hemorrhagic. On the surface of the duodenal part in contact with the duodenum are sparsely scattered opaque white areas of fat necrosis. Microscopic examination of a section from the duodenal part of the gland shows that newly-formed cellular connective tissue has in a small area replaced the glandular elements. Proliferation of cells has occurred in the adjacent interlobular tissue, which contains in abundance red blood-corpuscles, polynuclear leukocytes, and fibrin.

Should bile enter the pancreas after occlusion of the distal end of the diverticulum of Vater, its only opportunity for escape would be by way of the lesser pancreatic duct. In order to reproduce this condition, in the following experiments the duodenum was not opened, but the duct was exposed where it approaches the intestine, ligated close to the duodenum and partially cut across. By means of a syringe with a blunt nozzle bile was injected into the distal end of the duct, which was then ligated.

EXPERIMENT VI. Into the larger duct was injected 5 c.c. of bile obtained by puncture from the dog's gall-bladder. The animal died twenty-four hours later. The peritoneal cavity contains an excess of fluid. Opaque white areas of fat necrosis are numerous upon the surface of the duodenal part of the pancreas and in the immediately adjacent fat of the duodenal mesentery. Similar foci are present in both layers of the mesentery near the stomach and pancreas and in the fat in contact with the splenic part of the gland. The interstitial tissue of the duodenal part over an area near the orifice of the

larger duct, 2.5 cm. in width, shows deep red hemorrhagic infiltration. The parenchyma throughout the gland is mottled, small dull red areas alternating with more normal gray-yellow gland substance. The hemorrhagic appearance of the parenchyma is most marked in the duodenal part of the gland where there are homogeneous dull red areas of considerable extent. Both lungs contain extensive deep red areas which are fairly firm in consistence and exude very abundant frothy serum. Microscopic examination of all parts of the pancreas shows the presence of numerous foci of necrosis. The gland-cells have assumed a hyaline appearance and have lost their nuclei. The blood-vessels in these areas are widely distended, and at times there is abundant extravasation of red blood-corpuscles. Polynuclear leukocytes in moderate number are seen between the necrotic cells. The interlobular tissue is in many places much distended, containing red blood-corpuscles, polynuclear leukocytes, and fibrin.

EXPERIMENT VII. The operation already described was repeated, and 3.7 c.c. of bile obtained from the gall-bladder of the same dog was injected into the larger duct. The animal was killed three days later. Upon the surface of that part of the pancreas which is in contact with the duodenum and in the fat immediately adjacent to the splenic part are a few opaque areas of necrosis. The pancreas is very firm throughout. On section the glandular lobules are found to be separated by septa of interstitial tissue which are firmer and thicker than usual, and, near the transition of the larger duct, infiltrated with blood. In the duodenal and splenic parts of the gland microscopic examination demonstrates within the lobular tissue numerous small areas where newly-formed cellular interstitial tissue replaces groups of acini. The interlobular tissue is infiltrated with red blood-corpuscles, and often contains in great abundance polynuclear leukocytes and fibrin.

SYNOPSIS OF EXPERIMENTS.

I. *Duodenum opened and duct injected.*

	Amount of bile.	Mode of death.	Pancreas.	Fat.
No. 1,	5 c.c.	Killed in 7 days.	Hemorrhagic inflammation and sclerosis.	Fat necrosis near pancreas.
" 2,	5 c.c.	Killed in 5 days.	Hemorrhagic inflammation and sclerosis.	Fat necrosis.
" 3,	5 c.c.	Died in 20 hours.	Hemorrhagic inflammation.	Extensive fat necrosis.
" 4,	3 c.c.	Killed in 7 days.	Slight hemorrhagic infiltration.	Slight fat necrosis.
" 5,	2.5 c.c.	Killed in 4 days.	Slight hemorrhagic inflammation and sclerosis.	Slight fat necrosis.

II. *Duct opened, injected, and ligated.*

" 6,	5 c.c.	Died in 24 hours.	Hemorrhagic inflammation.	Fat necrosis.
" 7,	3.7 c.c.	Killed in 3 days.	Hemorrhagic inflammation and sclerosis.	Slight fat necrosis.

The injection of 5 c.c. of bile into the pancreatic duct caused hemorrhagic inflammation of the gland in four dogs, two of which died within twenty-four hours after the operation. Death did not follow the use of smaller amounts, and the changes produced in the organ were less wide-spread and severe. In every case necrosis of the adjacent fat accompanied the lesion of the pancreas, and in the two instances in which death occurred spontaneously foci of necrosis were abundant and disseminated. In Experiment No. 1, though the entire splenic arm of the gland was the seat of an intense inflammatory reaction, cover-slips and cultures demonstrated the absence of bacteria. The presence of bacteria in the pancreas of dog No. 2, which died twenty hours after the operation, is not surprising, since the injection was made through the duodenal orifice of the duct.

Microscopic examination confirmed the diagnosis of hemorrhagic pancreatitis, and demonstrated the identity of the experimental lesions with that which occurs in human cases. The injected bile first causes necrosis of parenchymatous cells with which it comes in contact. They lose their nuclei, and their protoplasm assumes a homogeneous hyaline appearance and stains deeply with eosin. The injurious action of the irritant upon the bloodvessels is manifested by the occurrence of hemorrhage into the necrotic areas. An inflammatory reaction now ensues and is characterized by the accumulation of polynuclear leucocytes and fibrin in the interstitial tissue and in the necrotic parenchyma. The necrotic material undergoes disintegration, and a rapid new growth of interstitial fibrous tissue, in part or wholly, replaces it. Where death does not rapidly follow the primary effects of the operation opportunity is given for the occurrence of secondary changes in the gland. The experimental lesion is not in all cases so extensive as that recorded in the accompanying autopsy report. In these experiments a single injection of bile is made, while in the human case bile is repeatedly poured into the organ.

CONCLUSIONS. 1. A gallstone impacted in the diverticulum of Vater may occlude the common orifice of the bile-duct and duct of Wirsung and convert them into a continuous closed channel. Bile enters the pancreas by way of the pancreatic duct, and the pancreas becomes the seat of inflammatory changes characterized by necrosis of the parenchymatous cells, hemorrhage and the accumulation of

inflammatory products. Anatomic peculiarities of the diverticulum of Vater do not permit this sequence of events in a small proportion of individuals.

2. Injection of bile into the pancreatic duct of dogs causes a necrotizing hemorrhagic inflammation of the pancreas resembling the human lesion, and, like it, accompanied by fat necrosis. Necrosis of the parenchymatous cells and hemorrhage represent the primary action of the bile; an inflammatory reaction rapidly follows.

3. The frequent association of cholelithiasis with hemorrhagic and gangrenous pancreatitis is the result of gallstone impaction at the orifice of the diverticulum of Vater and penetration of bile into the pancreas.

FILARIAL LYMPHATIC VARIX.

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SINCE Demarquay[1] discovered embryo filariæ in chylous fluid from the tunica vaginalis, numerous observers, in great part English physicians residing in the British colonies, have demonstrated the frequency with which filarial infection occurs in tropic countries. In 1868 Wucherer[2] noted the presence of filariæ in chylous urine, and in 1879 Lewis[3] recorded their presence in the blood. It was not until 1876 that Bancroft,[4] examining a suppurating lymphatic varix of the arm, found the adult female worm to which Cobbold, recording the discovery, gave the name Filaria bancrofti.

The parasite has a wide geographic distribution and infects a large proportion of the population of many tropic countries. Manson[5] has collected observations demonstrating the prevalence of filaria on the East and West African Coasts, in Morocco, India, Ceylon, the islands of the South Pacific, British Guiana, and the West Indies. It has been observed in many other tropic countries. In Cochin, a district of Southern India, Manson found one-third of the inhabitants infected, and in Samoa one-half of those examined, while Thorpe[6] in the Friendly Islands found filarial hematozoa in the blood of 32 per cent. of the natives. A large proportion of infected individuals appear to be in good health, but a variety of pathologic conditions with which the parasite has been found associated are undoubtedly caused by its presence.

[1] Gaz. Méd. de Paris, 1863, xviii. p. 665.
[2] Gazeta Medica da Bahia, December 15, 1868, p. 97.
[3] Indian Annals of Medical Science, Calcutta, 1873–74, xvi. p. 504.
[4] Cobbold. Lancet, 1877, lxviii. pp. 70 and 495.
[5] Tropical Diseases. London, 1900.
[6] British Medical Journal, 1896, ii. p. 922.

Numerous investigations have shown that Filaria bancrofti requires two hosts in order to complete the cycle of its life-history. Embryo filariæ are withdrawn from the human body by a blood-sucking insect, the mosquito, and in its body undergo a series of developmental changes. The adult male and female filaria, macroscopic nematodes several inches in length, have been repeatedly found within the dilated lymphatic vessels of the human host. Almost the entire body cavity of the female is occupied by a uterus filled with ova and embryo parasites in various stages of development. The minute worm-like embryos, containing no recognizable organs and enclosed in a delicate sheath, are poured in great numbers into the lymphatic vessels, and hence reach the bloodvessels, where, owing to their small diameter, about that of a red blood-corpuscle, they circulate freely through the capillary vessels.

Manson[1] has shown that when blood containing embryo filariæ is drawn into the stomach of a mosquito the parasite loses its sheath, and by active movements makes its way through the stomach wall into the thoracic muscles of the insect, where it undergoes changes by which it acquires a digestive tract and other rudimentary organs. Low[2] has recently found that the parasite makes its way into the head of the mosquito and lies in the loose connective tissue below the cephalic ganglion and salivary duct, finally penetrating the proboscis, where it may be demonstrated by appropriate sections. Here two worms are almost constantly seen together. Manson's early investigations have been, it is well known, the incentive for much of the research which has demonstrated that the mosquito is an intermediate host of the malarial parasite, and transfers the protozoon from one human host to another. The discovery of the partially developed parasite in the proboscis of the mosquito indicates that the filaria follows the analogy of the malarial organism, and is transmitted from one individual to another by certain species of mosquitoes in which it passes the entire period of its existence outside the human body. Investigations of James[3] have confirmed and extended Low's observations.

Low studied the development of filaria in the mosquito Culex ciliaris; James, in Culex microannulatus and Culex albopictus. James has shown that mosquitoes of the genus Anopheles may har-

[1] Cobbold. Lancet, 1878, lxix. p. 69.
[2] British Medical Journal, 1900, i. p. 1456.
[3] Ibid., ii. p. 533.

bor filariæ, and has traced the development of the parasite in Anopheles rossii. It is, therefore, not improbable that a considerable number of different species may act as intermediate host to Filaria bancrofti. Every infected individual becomes a source of danger to the community in which he lives should an appropriate species of mosquito thrive in the same locality. Constantly increasing intercourse between the United States and tropic countries, notably the West Indies and the Philippine Islands, give increased importance to this possibility.

Filarial infection is prevalent throughout the West Indies. Guitéras[1] found filariæ in the blood of four Cubans residing at Key West. A case described by Young[2] was that of a resident of Jamaica. The disease seems to be particularly prevalent in the Windward and Leeward Islands. Flint[3] has reported a case from the Island of St. Kitts. Manson[4] examined specimens of blood from twenty-eight inhabitants of the Islands of St. Kitts and Montserrat, and in six found filariæ. In 152 specimens from the Island of St. Vincent filariæ were found in six. Galgey[5] has found similar parasites numerous upon the Island of St. Lucia. The patient of Lothrop and Pratt[6] had lived on the Island of Barbados. The patient whose case is to be described was a native of the Island of St. Thomas.

There is little doubt that the disease prevails to a limited extent in the Southern States, and in a number of instances infection has been acquired within this country. Guitéras found filariæ in the blood of a mulatto, a native of Charleston, S. C., who, though he had lived only in South Carolina and Georgia, suffered with chyluria. In the blood of a second negro suffering with chylous hydrocele Guitéras found filariæ. De Sassure[7] has described twenty additional cases of filarial infection occurring in residents of Charleston, S. C. In all but two cases the infection was undoubtedly acquired within the United States. Mastin[8] records the case of a white man who had never lived outside of Mobile, Ala., and its immediate vicinity; filariæ were found in chylous fluid withdrawn from the tunica vaginalis. Henry[9]

[1] Medical News, 1886, xlviii. p. 395.
[2] British Medical Journal, 1897, i. p. 1037.
[3] New York Medical Journal, 1895, lxi. p. 737.
[4] British Medical Journal, 1897, ii. p. 1837.
[5] Ibid., 1899, i. p. 146.
[6] American Journal of the Medical Sciences, 1900, cxx. p. 525.
[7] Medical News, 1890, lvi. p. 704.
[8] Annals of Surgery, 1888, viii. p. 321.
[9] Medical News, 1896, lxviii. p. 477.

describes a case of filarial chyluria in a girl who had lived only in South Carolina, Florida, and Pennsylvania. Two cases of chyluria with filariæ in the urine are described by Slaughter.[1] The infected individuals had for at least twenty years lived in Virginia, a short distance from Washington, and gave no history of having visited any tropic country. Even more surprising is the case described by Dunn.[2] His patient, who had suffered with filarial chyluria, had never been outside of Pennsylvania, and had spent almost her entire life in Philadelphia. Winn[3] discovered filariæ in the urine of a patient suffering with chyluria who had resided in the Northern and Western States.

A case of filarial infection imported from the West Indies has been studied recently in the Pathologic Laboratory of the Johns Hopkins Hospital. Since the condition is so rarely encountered in this locality, it was not suspected during life and, unfortunately, no observations were made upon the living parasite. Few autopsies have been performed on subjects of filariasis, and the pathology of the associated conditions is not well understood.

Clinical History. Male, aged twenty-four years. The patient was admitted to the Johns Hopkins Hospital, in the service of Dr. Halsted, complaining of abdominal pain and distention. No very definite personal history was obtainable. He was born of Danish parents on the Island of St. Thomas, one of the Danish West Indies. Since the age of fourteen he had been a sailor, and for a number of years visited different ports of the West Indies. For the past few years he had lived in this country. He has repeatedly had what he describes as "spasms," and has had, he says, a hernia for eight years.

The patient was brought to the hospital in an ambulance Sunday, March 3d. He was well and able to work until the preceding Thursday, when, in the evening, he had a chill and went to bed. During the "spasm" which followed, his hernia, he says, came down and has not since been reduced, though an attempt was made by a physician. Since Friday he has had severe abdominal pain and has vomited frequently, the vomitus having, it is said, a fecal odor. The bowels had not moved since last Thursday; urine was voided with some difficulty and pain.

The patient is a sparely-built man, with swarthy complexion. His temperature on admission was 104.2° F.; the pulse, of poor volume, is 136 to the minute. The percussion note over the lower right back and axilla is flat and high-pitched, and the breath sounds are distant. The abdomen is symmetri-

[1] Medical News, 1891, lix. p. 649.
[2] Transactions of the College of Physicians of Philadelphia, 1898, xx. p. 80.
[3] Indiana Medical Journal, 1896, xiv. p. 409.

cally distended and tympanitic; the spleen is not palpable. White blood-corpuscles number 20,800. In the right groin is a visible tumor consisting of two parts. One part, a rounded mass lying immediately below Poupart's ligament, is 3 cm. in diameter and tender to the touch. It gives no impulse on coughing, but appears to have a slightly resonant percussion note, and was thought to be a strangulated femoral hernia. The second part of the tumor, lying below the saphenous opening, measures 8 by 3 cm., and feels like a mass of enlarged lymphatic glands. Both testicles can be felt, and the left epididymis is somewhat smaller than the right.

An exploratory incision under cocaine anesthesia was made over the supposed hernia. It was found to consist in part of a mass of dilated channels containing clotted blood, often of chocolate color, in part of denser tissue of spongy texture. This new growth apparently followed the femoral vessels and extended a short distance along the saphenous vein. A part of the mass was removed, the wound was partially closed, and iodoform gauze was inserted into its lower angle.

Since the symptoms indicated the existence of general peritonitis, on the following morning an exploratory incision was made in the median line of the abdomen. Pus and fibrin were found in all parts of the peritoneal cavity, but careful examination of the abdominal viscera failed to reveal any cause for the peritonitis present.

The patient remained weak and restless after the operation. The white blood-corpuscles, counted three times, numbered from 16,400 to 21,000; the temperature fell to 98° F. after the second operation, but rose to 103.9° shortly before death, which occurred on the following day. The urine contained a small quantity of albumin and a few casts, but other alterations were not noted.

Autopsy. The body is that of a sparely-built, well-nourished man. In the right inguinal region is a linear incision, the upper part of which is closed by silver wire; the lower part is open, and from it can be squeezed thin, turbid fluid. The exposed fat is deep red and injected. Through the abdominal wall near the median line is a second closed incision.

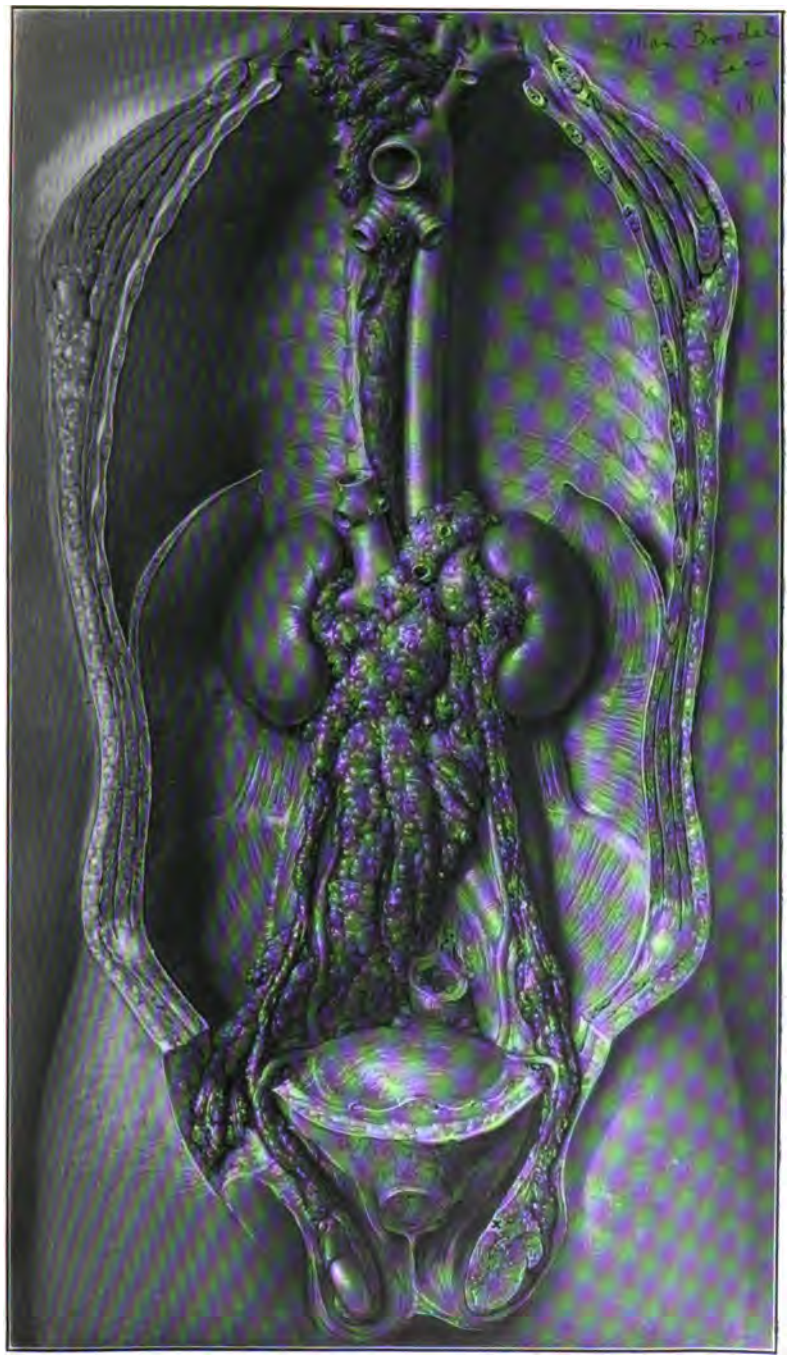
The peritoneal cavity contains about 50 c.c. of opaque, yellow fluid; the omentum and several loops of the intestine are lightly adherent to the anterior abdominal wall near the wound, and in places adjacent peritoneal surfaces of the omentum and intestine are lightly held together by fibrinous material. The peritoneal surface is dull, and here and there is covered by fibrino-purulent exudate in small amount. Minute vessels are injected and subserous ecchymoses are numerous. The appendix curled up in the iliac fossa is normal in appearance. The right pleural cavity contains no excess of fluid. The parietal and visceral surfaces are dull and lightly bound together by fibrinous exudate resembling that of the peritoneum and most abundant over the basal surface of the lung. The left pleural and pericardial cavities show no evidence of inflammation.

The heart weighs 270 grams; below the epicardium are numerous ecchy-

motic points; the valves are delicate. The lungs, resembling one another closely, are deep red in color and exude bloody serum, but are crepitant throughout; the bronchi are slightly injected; the surface of the liver is smooth and of a yellowish-red color, studded with minute ecchymoses; the spleen is not enlarged, weighing 150 grams; the capsule is thickened and fibrous in places; the stomach and intestines are normal throughout; the pancreas is firm in consistence, compact in texture, and of a uniform grayish-yellow color. Near the upper border of the head of the organ is an enlarged lymph gland, hemorrhagic on section and 1.5 cm. in diameter. The mesentery contains lymphatic glands which are firm, gray-white, and occasionally 1.5 cm. in diameter. No abnormality of the lacteal vessels is noted.

After exposing the retroperitoneal tissue by removal of the above-named organs is seen a diffuse and extensive new growth which was previously inconspicuous. (See Plate.) It occupies the entire space between the kidneys and extends along the renal vessels into the hilum of the right. It is in direct contact with both adrenals, but does not invade them. It extends downward in front and on either side of the aorta and vena cava as far as the promontory of the sacrum, and has an average width of 5 cm. and a thickness of only 1 to 1.5 cm. An extension passes into the pelvic cavity to the right of the median line and forms a flattened mass lying behind the ureter and between the bladder and pelvic wall, having here an average thickness of about 2 cm. The tumor tissue completely embeds the aorta and vena cava below the level of the renal vessels, and sends a lappet in front of the right ureter. It can be readily dissected from the structures with which it is in contact. When the adherent areolar tissue and fat are removed from its surface the appearance is that of a mass of thin-walled dilated and tortuous vessels containing dark, thrombus material. Convolutions projecting forward give a nodular aspect to the surface. The tissue is flaccid in consistence but tough, and on section is found to consist of dilated trabeculated channels, usually 2 to 5 mm. in diameter, lined by smooth endothelium and containing firm thrombus material of dark red or reddish-brown color. They are held together by a varying amount of fibrous tissue, in which fat is abundant. A flattened continuation of the tumor follows the femoral vessels under Poupart's ligament, covering them for a short distance and lying in the wall of the wound previously mentioned. In this tissue is embedded a lymph gland about 1.5 cm. in diameter. From the tumor mass in the region of the kidney a strand of dilated thrombosed channels resembling those elsewhere passes down along each spermatic vein to the testicle, and forms in contact with the epididymis a spongy fibrous mass which is larger on the left than on the right side.

To the right of the aorta a continuation of the varicose tissue within the abdomen extends upward through the diaphragm and expands slightly immediately above to form a smooth, cylindric mass 2 cm. in diameter, composed of dilated thin-walled sinuses, the lumina of which are broken by irregular trabeculæ and contain brownish thrombus material. This rela-



The accompanying drawing, which accurately reproduces the appearance of the lymphatic varix described, has been made by my friend, Mr. Max Brödel, to whom I desire to express my obligation. It shows the entire varix in situ. A section for microscopic examination, from the position marked ×, immediately above the left epididymis, contained the adult worm occupying a dilated lymphatic vessel.

tively smooth mass lies to the right of the aorta for a distance of 10 cm. above the diaphragm, and then becoming irregular in outline, as if composed of separate dilated channels, passes behind the arch of the aorta to the left side of the esophagus and trachea. The dilated vessels which form it pass between the left subclavian, left carotid and innominate arteries, and form in front of them a small mass resembling the tumor tissue elsewhere. In removing the specimen the veins at the base of the neck were cut so that their relation to the tumor mass, which evidently represents the enlarged varicose thoracic duct, could not be definitely determined. At one point there is a communication between a vein occupying approximately the position of the left subclavian and the varix. The orifice in the wall of the vein is about 2 mm. in diameter, and gives entrance to a dilated channel which is filled almost to the surface of the vein by thrombus material resembling that found elsewhere in the dilated channels.

The kidneys, ureters, and bladder appear to be normal; the aorta is smooth throughout, and the inferior vena cava is normal.

Microscopic Examination. Sections made from various parts of the varix-like tumor show that it consists of thin-walled vessels held together by loose alveolar tissue containing fat. The vessel walls are formed in great part by fibrous tissue, but contain smooth muscle, often in considerable quantity. (Hypertrophy of muscular tissue is described by Lothrop and Pratt.[1]) The lining endothelium is represented by oval nuclei seen at intervals. These vessels have not the structure of veins or of arteries. Occasionally the smaller channels do not have distinct walls, and are simply dilated spaces within the connective tissue. The lumina are filled with red blood-corpuscles and polynuclear leukocytes in great number lying in a rich network of fibrin. Lymphoid cells occur in small number, and here and there are large endothelioid cells with vesicular nucleus. Sections stained by Weigert's fibrin stain demonstrate the presence of diplococci in great numbers, both free and within leukocytes. The dilated lymphatic vessels are embedded in fibrous tissue which is infiltrated with polynuclear leukocytes, often very numerous and mingled in places with fibrin and red blood-corpuscles. Occasionally the tissue is denser and more fibrous and contains lymphoid cells.

A section through the varix in contact with the left epididymis shows dense interstitial tissue containing numerous lymphoid, plasma, and eosinophile cells. The section passes through a dilated lymphatic vessel which contains what is immediately recognizable as at least one much-coiled nematode worm cut many times. The body is formed by a musculocutaneous tube covered by a thin cuticle. Its most conspicuous anatomic feature is the bilobed uterus filled with ova and embryos in various stages of development. Some of the latter are coiled up within an oval sac, while others lie stretched out parallel to one another. In all sections the alimentary canal is recognizable as a slender tubule whose cells contain brown pigment. Several sections appear

[1] Loc. cit.

to belong to a second smaller worm. Its digestive tract is larger, and there is within the musculocutaneous body only one other tubular organ.

Sections from various organs were carefully examined for embryo filariæ. In a small hepatic vein was found a portion of a small worm-like body composed of a cuticle surrounding a central nucleated strand and identical in structure with the intra-uterine embryos.

Bacteriologic Examination. Stained smear preparations of the exudate in the pleural and peritoneal cavities contain very numerous capsulated lanceolate diplococci. Cultures from the lymphatic varix studied by Mr. Warfield Longcope contain diplococcus lanceolatus in pure culture. Diplococcus lanceolatus and staphylococcus pyogenes albus were obtained from the peritoneal cavity.

Pathologic Diagnosis. Filariasis; lymphatic varix involving thoracic duct, retroperitoneal lymphatic vessels of the abdomen and pelvis, and lymphatic vessels of the spermatic cord and of the right groin; adult Filaria bancrofti within a dilated lymphatic vessel; embryo filaria in a branch of the hepatic vein. Terminal infection of lymphatic varix with diplococcus lanceolatus; fibrino-purulent inflammation of the peritoneum, right pleura, and tunicæ vaginales.

A clinical condition referable to the parasite was the presence of a tumor mass in the right groin, which, according to the patient's statement, had been for eight years supposed to be a hernia. Autopsy demonstrated the existence of an immense plexus of enormously dilated lymphatic vessels lying in the abdomen and pelvis in front of the vertebral column. Continuous with this plexus was the distended varicose thoracic duct passing beside the aorta to the base of the neck. Dilated lymphatics held together by fibrous tissue followed both spermatic veins as far as the epididymis, and a similar mass of lymphatic vessels passed with the femoral vein and artery under Poupart's ligament and formed the mass which, during life, was mistaken for a hernia. An adult filaria occupied a dilated lymphatic vessel near the right epididymis, and a single embryo was found in a bloodvessel of the liver. The entire lymphatic varix was the seat of acute inflammation characterized by the accumulation of polynuclear leukocytes in the distended vessels and in the intervening tissue. The lymphatic vessels were filled in great part with blood, and had everywhere undergone thrombosis. Bacteriologic examination demonstrated infection with diplococcus lanceolatus; secondary infection of the serous cavities in contact with the varix had occurred, and death resulted with acute fibrino-purulent inflammation of the peritoneum, right pleura, and both tunicæ vaginales.

Since the parasites in the preceding case were not studied during life, and were only observed in sections of the tissues obtained at autopsy, it was not possible to determine the details believed by Manson to distinguish different species of filaria. The sexually mature parasite discovered by Bancroft was described by Cobbold and given the name Filaria bancrofti. This nematode is now known to be the parent form of the embryonic worms which Lewis had previously found in the blood. Filaria sanguinis hominis, the name originally proposed by Lewis and most commonly employed to designate filarial hematozoa, being trinomial is not acceptable to zoölogists as a designation for the species. Manson,[1] who has carefully studied embryo filariæ from the blood of many individuals inhabiting widely separated tropic countries, has arrived at the conclusion that there are at least four, possibly five, distinct species of filaria, embryos of which circulate freely in the blood. His distinctions concern the disappearance of the parasite from the blood during certain periods of the day, its size, the presence or absence of an enveloping sheath and certain details of shape and structure.

Manson[2] discovered the remarkable fact that the filarial embryos disappear from the blood during the day, though they may be found in large numbers during the night. Examinations repeated at intervals during the day and night demonstrate their periodic disappearance from the cutaneous circulation. Appearing at 6 or 7 o'clock in the evening, and gradually increasing in number, they reach a maximum at midnight. A gradual diminution in number then occurs, and at 8 or 9 o'clock in the morning they have entirely disappeared. Subsequent observers have confirmed the occurrence of this phenomenon. From observation made upon an infected individual who committed suicide at 8.30 A.M., Manson[3] thinks it probable that the majority of the parasites accumulate during the day in the lungs. Stephen Mackenzie[4] made the important observation that this periodicity might be reversed by reversing the habits of the infected individual, causing him to sleep during the day and remain awake and take his meals during the night. Filarial embryos then become abundant during the day, but are absent from the cutaneous blood during the night.

[1] Lancet, 1891, i. p. 4, and British Medical Journal, 1897, ii. p. 1837.
[2] Transactions of the Pathological Society of London, 1881, xxxii. p. 285.
[3] British Medical Journal, 1899, ii. p. 644. [4] Loc. cit.

Manson subsequently found that the occurrence of this periodic disappearance of filariæ is not a constant phenomenon, even when the habits of the infected individual undergo no purposeful change. In the great majority of cases, notably in individuals infected with various forms of lymphangiectasis, chyluria, and chylous hydrocele often demonstrably associated with the worm described by Bancroft in the infected lymphatics, the phenomenon of periodicity occurs, and to this parasite Manson has given the name Filaria sanguinis hominis nocturna, the prior binomial name being Filaria bancrofti. In the blood of three negroes from the west coast of Africa, Manson[1] found an embryo which morphologically resembled the nocturnal form, but presented a reversed periodicity, appearing during the day, though absent during the night. Manson designates the parasite Filaria sanguinis hominis diurna. It is not inconceivable that some peculiarity of the infected individuals may have caused this alteration of the parasite. Manson's suggestion that Filaria loa is a parental form of this embryo has very little in its favor.

In natives of the west coast of Africa, Manson found a third variety of hematozoa which does not disappear from the blood during either day or night, and has been designated by him Filaria sanguinis hominis perstans. It is much smaller than the previously mentioned parasites, possesses no sheath, is more actively motile, has a truncated tail, presents certain peculiarities of the oral apparatus and does not possess the granular aggregation which in other forms has been found near the mid-part of the body.

In blood obtained from inhabitants of an island of the West Indies, St. Vincent, Manson[2] has described what he believes to be a fourth species, and has given it the name Filaria demarquayi. It has a pointed tail and is shaped like Filaria nocturna, but is less than half as large and has no sheath. It is present in the blood during the day and night. In the blood of the aboriginal Indians from the interior of British Guiana he thinks he has distinguished still a fifth variety. This was associated with a blunt-tailed embryo which he identified with his Filaria perstans of the west coast of Africa, the two being often found together on the same slide. This fifth variety, which he calls Filaria ozzardi, resembles very closely his Filaria demarquayi, and he thinks may be identical with it, though characterized by certain pecu-

[1] Lancet, 1891, i. p. 4.

[2] British Medical Journal, 1897, ii. p. 1837.

liarities of shape, size, and staining reaction which he does not clearly define. Galgey[1] found on the Island of St. Lucia what he believed to be Filaria demarquayi, and concluded that it was identical with specimens of Filaria ozzardi sent to him for comparison.

At the postmortem examination of two British Guiana aborigines whose blood contained the two forms designated by Manson, Filaria perstans and Filaria ozzardi, Daniels[2] found in one case in the mesentery and in the fat at its base, in the other in the pericardial fat as well, male and female nematodes, which he believes are the parental forms of Filaria perstans. The uterus of the female contained only blunt-tailed embryos. The adult worm was more slender than Filaria bancrofti, and, unlike the latter, was provided with a slightly bulbous tail having a thickened cuticle prolonged into two triangular appendages. In a third case of similar character Daniels[3] found, in addition to what he believed to be adult Filaria perstans, a female and portion of a male located in the subperitoneal connective tissue of the anterior abdominal wall. The female closely resembled in size and shape Filaria bancrofti, but since the tail was slightly bulbous Daniels believed it to be a different species, the parent form of the blunt-tailed embryo, Manson's Filaria ozzardi.

The specific peculiarities of the filaria described evidently require further investigation. Periodic disappearance from the blood may be dependent upon peculiarities of the host; male and female embryos of the same species may have slight morphologic differences.

In the left ventricle of a child who died in Rio de Janeiro, Magalhaes[4] found male and female sexually mature filariæ, of which he has given a careful description. They are much larger than Filaria bancrofti and differ in details of structure. The child's blood was not examined; from analogy it is not improbable that the parasite discharged embryo worms into the blood, but their relation to the forms which have been described by Manson is entirely unknown.

Filariæ were discovered by Demarquay in chylous hydrocele fluid. Wucherer found embryos in the urine from a case of tropic chyluria; Lewis, who first found filariæ in the blood, observed this frequent association with chyluria and with the so-called lymph scrotum, a

[1] British Medical Journal, 1899, i. p. 145.
[2] Ibid., 1898, i. p. 1011.
[3] Ibid., 1899, i. p. 1459.
[4] See von Linstow, Centralbl. f. Bakt., 1892, xii. p. 88.

condition in which the scrotum contains a mass of tortuous and dilated lymphatic vessels, the tunica vaginalis being often distended with serous or chylous fluid. Subsequent observations have demonstrated the association of filaria with various forms of lymphatic varix. These occur in a variety of situations, in the groin, in the axilla, and more deeply seated within the abdomen and thorax. Embryo filariæ are found both in the fluid from the varix and in the blood of the infected individual, while in a considerable number of cases (collected by Lothrop and Pratt) the adult worm has been found. When it has been possible, as in the present case, to determine the location of the sexually mature parasite it has been found to occupy a dilated lymphatic vessel. The parasite associated with the above-named conditions has been identified as Filaria bancrofti, whose embryos appear in the blood at night—Filaria sanguinis hominis nocturna of Manson. Though in the case herewith described it was not possible to determine the specific peculiarities of the filaria observed in sections of the hardened tissues, there is no reason to doubt its identity with that which has been constantly found associated with the same lesion.

A very large proportion of those who harbor hematozoal filariæ are apparently in perfect health. Under what condition the worm becomes harmful to its host is not understood. The embryos discharged by the female into the lymphatic vessels reach the blood presumably through the right or left thoracic duct, and, it appears, circulate freely without apparently producing any harmful effects. The various associated lesions have been referred to the presence of the adult worm in the lymphatics. Few autopsies have been performed on the subjects of filarial disease, and the pathology of chyluria, chylous hydrocele, ascites, and various forms of lymphatic varix of the scrotum, of the groin, and of the axilla is not fully explained.

A case of filarial hematochyluria was carefully studied during life by Stephen Mackenzie,[1] and at autopsy there was found an enormous lymphatic varix very closely resembling that of the above described case. A mass of dilated lymphatic sinuses occupying the entire space between the kidneys extended from the diaphragm to the bifurcation of the aorta and was continuous below with lymphatic tissue lying upon the iliac arteries. The thoracic duct formed by the union of several dilated pouched channels arising from this mass was distended, and at

[1] Loc. cit.

a point one and a half inches above the diaphragm was filled by a loose clot. The terminal part of the duct appeared to be pervious. Finding the lymphatics near the kidney greatly dilated Mackenzie thought it probable that within the kidney, between the lympathic and urinary apparatus, there was a communication by which chylous lymph entered the urine. The bladder appeared to be normal; chyle and blood had, however, entirely disappeared from the urine three months before death.

Much more decisive regarding the pathology of chyluria is a case reported by Havelburg.[1] The patient had for six months suffered with chyluria, and filariæ had been found in the urine and at night in the blood. A partial autopsy disclosed an immense abdominal tumor extending from the kidneys to the pelvis and composed of varicose projecting sinuses containing chyle. The tumor was in intimate contact with the left side of the bladder. On opening this organ there was found in the mucosa opposite a perforation from which milky fluid could be squeezed.

Extensive lymphatic varices similar to those already cited are described by Manson,[2] Ewald,[3] and Young.[4] In Manson's case the terminal two or three inches of the thoracic duct were entirely occluded, but below this level the lumen was patent, though occupied by a firm thrombus. The patient of Young suffered with a lymphatic varix of the scrotum, upon which two unsuccessful operations were performed. Projecting tumors of a similar nature were present in both groins. At autopsy a huge mass of dilated varicose lymphatics was found in front and on either side of the lumbar vertebræ and extended into the pelvis behind the bladder; prolongations extended into the scrotum and projected in the groins. The thoracic duct was greatly dilated and, as Young believed, occluded only at its orifice. Filariæ had been repeatedly found during the night, and three adult filariæ were obtained from the varix of the left groin, while seven were present in the lymphatics of the right spermatic cord. The case resembles very closely that described in the present paper.

In the cases cited, lymphatic vessels within the abdomen, in front of the vertebral column, have been transformed into an immense varicose tumor. The thoracic duct continuous with this tumor mass has been

[1] Virchow's Arch., 1888, lxxxix. p. 365.
[2] Davidson's Hygiene and Diseases of Warm Climates, p. 814.
[3] Deutsch klin. Wochenschr., 1888, p. 624. [4] British Medical Journal, 1897, i. p. 1037.

greatly dilated, and in several instances its terminal part has been occluded. The presence of this lymphatic varix, from which extensions lie in contact with the wall of the bladder and pass through the inguinal canal into the scrotum and under Poupart's ligament into the groin, explain the clinical manifestations of filarial infection. The inguinal masses (Manson's so-called "varicose groin glands") form part of an extensive varix, and may readily be mistaken for femoral herniæ. A similar extension into the scrotum, associated perhaps with rupture of thinned and dilated lymphatics into the tunica vaginalis, gives rise to the condition known as nevoid elephantiasis of the scrotum, lymph scrotum, or chylocele. The case of Havelburg seems to show that chyluria may be the result of actual rupture of dilated lymphatic vessels into the bladder.

Recorded cases of filarial varix do not afford a satisfactory explanation of its pathogenesis. Mackenzie, Manson, and Young regard occlusion of the thoracic duct as an essential factor in its production. Manson suggests that this may occur as the result of mechanical plugging by a bunch of intertwined parent filariæ or as a consequence of inflammatory changes produced by the presence of filariæ in the lymphatic vessels. This explanation does not accord with a number of observed facts. Ligation of the thoracic duct in animals is not followed by the formation of lymphatic varices. In cases reported by Martin,[1] Renvers,[2] and Ormered[3] the thoracic duct was occluded by thrombosis or by thrombosis and partial obliteration of the left innominate and subclavian veins; there were chylous ascites and moderate dilatation of the abdominal lymphatics, but nothing resembling the filarial varices described. On the other hand, in the case described by Bryk[4] an extensive varicose condition of the abdominal lymphatics and of the lymphatics of the arms and legs as well was caused by a small tumor in the posterior mediastinum pressing upon the thoracic duct, but the condition did not resemble that which has been associated with filaria.

What part the right thoracic duct takes in the establishment of collateral circulation has not been shown. No dilatation of this channel has been noted in any of the cases mentioned.

[1] Cited by Dawson, "Obstruction of the Thoracic Duct or its Venous Outlet." Twentieth Century Practice of Medicine, New York, 1895, vol. iv. p. 645.

[2] Ibid. [3] Ibid. [4] Ibid.

A condition which has received little attention is well illustrated in the present case. The lymphatic vessels throughout the varix are filled not with lymph but with blood. The case of Mackenzie was one of hematochyluria. In Ewald's case the dilated lymphatics contained bluish-red clots. The suggestion of Manson that red blood-corpuscles are formed within the obstructed lymphatics is not supported by any evidence. The presence of blood within the dilated vessels suggests a regurgitation at some point of communication between the venous and lymphatic systems. Should the presence of adult filariæ bring about some change by which either temporary or permanent regurgitation might occur the production of extensive varicosity would resemble that which follows a fistulous communication between an artery and a vein. It is very improbable that artificial communications between the vascular and lymphatic systems are ever produced by filariæ. It is not inconceivable, however, that the presence of the adult parasite might produce alterations of the valves at the orifice of the thoracic duct. The formation of a varix and the presence of blood throughout it are not explained by mere occlusion of the duct; the facts at our disposal do not furnish an adequate explanation of these conditions.

Repeated febrile attacks often associated with evident lymphangitis form an important clinical feature of filarial varix and its various manifestations. In the present case a fatal termination followed acute fibrino-purulent peritonitis and pleurisy, and the entire varix was the seat of acute lymphangitis. The left pleural cavity, which, unlike the right, was not in immediate contact with the varicose thoracic duct, escaped. Both tunicæ vaginales were the seat of fibrino-purulent inflammation resembling that of the peritoneum and pleura. Bacteriologic examination demonstrated the presence of diplococcus lanceolatus within the varix and upon the inflamed serous surfaces. The mass of dilated lymphatics not improbably represents a point of least resistance and exposes the infected individual to the constant danger of secondary bacterial invasion. The suggestion of Manson, that death of the parent worm is a source of inflammation, seems improbable.

The constant presence of a peculiar species of parasite and its relation to the associated lesion leave little doubt concerning the etiology of lymphatic varices and the accompanying conditions

already considered. The relationship of filaria to the wide-spread tropic disease, endemic elephantiasis or elephantiasis Arabum, maintained by Manson and other writers, has not been so clearly established. In this disease repeated attacks of fever accompanying localized inflammatory edema are followed by a progressive hypertrophy of the cutaneous and subcutaneous fibrous tissue and in less degree of the intermuscular areolar septa. The new-formed tissue is dense and fibrous and contains numerous distended lymphatic vessels. Some writers, for example Hebra,[1] in his monograph on elephantiasis, do not distinguish between true elephantiasis and hypertrophies due to the presence of lymphatic varices. So-called nevoid elephantiasis or lymphatic varix of the scrotum is, for the reasons already discussed, doubtless caused by Filaria bancrofti. Manson summarizes as follows the facts which he believes show a causal relationship of the same parasite to true elephantiasis: (1) The geographic distribution of Filaria nocturna and elephantiasis Arabum correspond. (2) Filarial varix and elephantiasis frequently co-exist in the same district and, indeed, in the same individual. (3) Lymphatic varix of the scrotum often terminates in elephantiasis, while (4) elephantiasis of the leg has been observed to follow removal of a scrotal varix. (5) Both lymphatic varix, which is undoubtedly caused by Filaria bancrofti (Filaria nocturna), and elephantiasis are diseases of the lymphatics, and (6) are accompanied by the same type of recurrent lymphangitis.

Nevertheless, embryo filariæ are not necessarily found in the blood of those suffering of elephantiasis, and, indeed, Manson states, are less frequently present in the blood of such individuals than in unaffected natives of the some district. Manson has advanced the hypothesis that the lymphatics of the part are plugged by ova which have escaped from the parent worm before their complete development into slender worm-like embryos. This suggestion of filarial abortion, as he designates the process, is not supported by any direct evidence. He recognizes the fact that simple plugging of the lymphatics is not sufficient to produce inflammatory hypertrophy of the fibrous tissue, but thinks that recurring erysipelatoid inflammation in the congested area is an essential factor in the production of the disease.

Manson has suggested that the papular and pustular disease of the skin known as craw-craw, occurring on the west coast of Africa, is

[1] Wiener Klinik, 1885, xi. p. 217.

caused by the parasite which he designates Filaria sanguinis hominis perstans. Though O'Neil, who first described the condition, found a filaria-like worm in the pustules, the parasite has never been identified with any since discovered.

Manson found his Filaria sanguinis hominis perstans in three cases of "sleeping sickness" from the Congo, and suggested an etiologic relationship. As he points out, the prevalence of filarial infection in the locality makes an accidental association of the two conditions not improbable in these cases. Filariæ doubtless cause various forms of lymphatic varix, chyluria, and chylous hydrocele, but their further pathologic significance has not been established.

EXPERIMENTAL PANCREATITIS.

[Second Paper.]

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AND

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In a previous paper one of us (Flexner[1]) described, in some detail, the results of the injection into the pancreas, either through the duct of Wirsung or directly into the parenchyma, of various substances of an irritating or injurious nature. It was shown that a considerable number of substances—artificial gastric juice, formalin, solutions of caustic alkalies, suspensions of pathogenic bacteria—are capable, under these circumstances, of provoking in the dog severe and often rapidly fatal forms of pancreatitis.

The chief variety of pancreatitis met with was the hemorrhagic, which, running an acutely fatal course, associated with glycosuria, was attended with extensive peritoneal fat necrosis. The gross morbid appearances closely reproduced those found in human beings the victims of hemorrhagic pancreatitis.

Not all the experiments terminated fatally within a brief time. Some animals lived for several days, when the character of the pathologic condition might be altered, as, for example, in the sequestration of portions of the injured organ. When death was delayed for several weeks, cysts, abscesses, and partial scleroses of the organ were encountered.

[1] "Experimental Pancreatitis," Contributions to the Science of Medicine, Dedicated by his Pupils to William Henry Welch, upon the Twenty-fifth Anniversary of his Doctorate, Baltimore, 1899, and University Medical Magazine, Philadelphia, January, 1901.

The conclusions which were arrived at may be summarized as follows: "Experimental work upon pancreatitis has thrown light at least upon two forms of the disease occurring in human beings, namely, the suppurative and the necrotizing varieties. It is probable, also, that in this way we have gained additional information about the chronic indurative forms of pancreatitis, since it has been found that that condition seems to follow any of the procedures which are capable of setting up pancreatitis without leading to the immediate death of the animal. What is most needed is more light on hemorrhagic pancreatitis, and more especially is it necessary to determine whether or not inflammatory changes precede hemorrhage, or whether the hemorrhage is the cause of the inflammation; or whether, again, they are independent affections which are merely frequently coincident.

"The results of the experiments which have been given lead to the conviction that (1) hemorrhage *per se* is a common condition in all forms of pancreatitis; (2) when it is excessive it dominates the process; (3) it is usually more pronounced than the inflammatory lesions, and the two conditions may be separate and distinct in the same organ or parts of the organ."

The series of experiments to be reported in this place is intended to be a further contribution to the pathology of pancreatitis, and to bear especially upon the manner and progress, in time and sequence, of the degenerative injury and the inflammatory reaction. The effects of blood and blood-serum when brought into intimate relation with the secreting structures of the pancreas, without further injury to the organ, will be described, and the influence of the spleen upon the development of the complete picture of acute pancreatitis considered.

The histologic changes will be dealt with in some detail, and the association of glycosuria with traumatism and inflammation of the pancreas briefly mentioned. In order to secure comparison two experiments, following Opie's[1] demonstrations, have been made with injections of bile, and these will also be described.

SERIES I. *Acid injections.* This series is a repetition of a previous series given in the former paper. The injection of 1 per cent.

[1] "The Etiology of Acute Hemorrhagic Pancreatitis," Bulletin of the Johns Hopkins Hospital, 1901, vol. xii. p. 182.

solutions of hydrochloric acid were made into the duct in quantities varying from 5 to 10 c.c. The immediate effect was edema of the body and tail of the pancreas with, later, the appearance of coagulation (pallor and opacity) in the organ. The latter effect is produced in five to ten minutes. Punctiform hemorrhages may also appear quickly, as in Experiment No. 2, in which they occurred within thirty minutes. This experiment will be detailed as an example of this series.

The average duration of life in this series varied (excluding Experiments Nos. 5 and 6, to be mentioned again) from seventeen to twenty-three hours. In Experiments Nos. 1 and 2 the animals were chloroformed, as they were dying, and it was desired to secure fresh tissues. Six experiments in all compose this series.

Experiment No. 2. Operation consisted of opening the duodenum and injecting 5 c.c. 10 per cent. HCl into the duct of Wirsung.[1] Large, well-nourished dog. Morphin and ether anesthesia. Experiment completed November 13, 1900, 3 P.M. Injection entered splenic end of pancreas; the organ became at once edematous and very soon showed yellowish-white patches. Before the intestine could be closed hemorrhages began to appear in the injected area, the time since the injection being one-half hour or less. Chloroformed twenty-three hours later. The site of operation appeared as at its conclusion. The skin was dissected back and the muscular and peritoneal tissues dissected away so as to include the silver-wire sutures and a large pad of fat within the abdominal cavity, attached to the anterior abdominal peritoneum. This mass presented exquisite circumscribed fat necroses, surrounded by zones of hemorrhage. Within the peritoneal cavity were about 50 c.c. of bloody fluid, but the serosa was smooth and glistening. The omentum was perfectly spread over the intestines and showed, in the fat along the thicker fibrous bands carrying vessels, etc., numerous small necroses. The pancreas was covered by the omentum, but could at once be made out to be smaller and hemorrhagic. The gland proved to be enveloped in semi-fluid dark blood. On incising the organ it was found dark and sodden. Only in a few places could paler, less altered pancreatic tissue be found, the largest focus of this nature

[1] Flexner, op. cit., p. 752.

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[1] Flexner, op. cit., p. 752.

being the head in the mesentery next the duodenum. The hemorrhage extends into the adipose tissue in the mesentery about the duodenum and into the adjacent mesentery. Fat necroses, some small and others large (3 x 6 mm.), occurred in the adjacent fat. The fat necroses give the reaction for steopsin.

The dogs in Experiments Nos. 5 and 6 were operated on December 19, 1900, and chloroformed January 8th and 7th respectively. Each received 3 c.c. of the acid solution into the duct. No. 5 when opened showed old fibrous adhesions between pancreas, omentum, and liver. The mid-portion of the pancreas was atrophied and firm, and the whole organ appeared small in size. The peritoneum was clear. The splenic end of the pancreas of No. 6 was contracted to the size of a bean. On incising this node it contained, in its center, a small cyst with semi-fluid, clear, yellowish contents. The duodenal end of the organ was free and apparently normal.

Histologic Examination. The description of the changes in the acutely lethal cases of this series given in the first paper[1] needs very few additions to make it complete. The three processes, hemorrhage, necrosis, and inflammation, are intimately associated. Usually the hemorrhage is more extensive than the other phenomena, and often precedes them, or is present in parts of the tissue, causing swelling of the interstitial and interacinous connective tissues, and even total disintegration of the acini, without reaction. The disintegration may be complete, the extensively separated glandular cells being scattered irregularly among the red corpuscles. Frequently, however, the hemorrhage is accompanied by inflammatory reaction in the form of emigrated leukocytes, fibrin, etc. Again, in certain septa an inflammatory edema without hemorrhage is the chief lesion, and degeneration of the glandular substance may also be wanting. In these edematous foci much fibrin occurs. As completing the possibility of separate occurrence of the several processes may be mentioned extensive hyaline necrosis of the centers (especially) of the acini without, in some cases, any immediate reaction. Near by reaction may be present in the interstitial tissue or even around glandular degenerations.

The glandular degenerations take place in two ways—either by

[1] Op. cit., p. 761.

direct action of the irritant upon the acini at the end of the ducts, or by diffusion from the interlobular connective tissues along the edges of the acini. The degenerations are almost without exception of the hyaline variety; only rarely do the cells show excessive granulation with failure of nuclei or vacuolization. The hyaline cells may remain in connection with their undegenerated associates or become demarcated from them. Very soon leukocytes find their way into their midst. The hyaline cells sometimes coalesce, forming a uniform, homogeneous substance, with here and there a nucleus of the polyform type visible.

The extent of the hyaline degeneration is subject to great variation. Single cells, portions of cells, or commonly groups of cells tend to show this change, while again whole acini or lobules undergo the metamorphosis. Demarcating inflammation about the larger foci bring about the production of so-called necrotizing pancreatitis.[1]

Isolation of lobules may also result from hemorrhage alone. This may not infrequently be seen in parts of the gland in which the escape of blood has been great. The island—frequently a lobule—of pancreas may still preserve its staining.

The epithelium of the ducts is more resistant to the acid than the acinous cells. While the ducts may contain many blood-corpuscles, the epithelium may be quite intact. It may, however, show changes, such as coalescence or hyaline desquamation, but this is uncommon.

The condition of the bloodvessels has already been described.[2] As stated, thrombi are irregularly present. Rarely a large vein will be occluded, the arteries seem not to suffer, and it is not common to find even small vessels obliterated.

The connective tissue in the acute cases is quiescent or only secondarily affected.

The interlobular and peri-pancreatic adipose tissues show necroses. The extent of reaction about them, as compared with that about the dead pancreatic substance, is, to say the least, remarkable. Great masses of leukocytes surround the dead cells, which may still show fatty acid crystals. What is striking is the small extent to which the cells enter the interior of the dead fat-cells—a phenomenon suggesting negative chemotaxis of strong degree. Upon what

[1] Flexner, op. cit., p. 761.

[2] Op. cit., p. 762.

constituent this depends cannot be said. That the dead tissue as a whole is markedly positively chemotactic is shown by the extent of the cellular reaction, the free center being in strong contrast, as at most a few fragmented, emigrated cells are found in the interior. This marked degree of inflammatory reaction about fat necroses may explain, in part, the view held by Balser, Langerhans, Seitz, and E. Fraenkel, who regarded them as leading to inflammation, hemorrhage, and necroses of the gland,[1] a position now no longer tenable.

The chronic changes present considerable interest. They were very briefly considered in the first paper, and merit greater attention. Fortunately, the variety of experiments now performed makes it possible to add to the former description.

Of this series Case No. 6 offers the greatest value, as it is a marked example of partial chronic (interstitial) indurative pancreatitis of the perilobular type. Considerable portions of the gland—especially of the duodenal end and tail—have escaped. The sclerosed portion shows an overgrowth of connective tissue affecting chiefly the interlobular tissue. About large bloodvessels and ducts the tissue is scar-like, containing masses of hematoidin pigment and occasional groups of lymphoid cells. A mild cellular accumulation is present about the vessels, infiltrating their walls. The tissue immediately about the acini is more cellular, the cells being spindle-formed. The acini may be widely separated, and the connective tissue may penetrate between the glandular cells. When the parenchymatous cells are closely invested by fibrous tissue from without or disintegrated from the growth into the acini, they change in character, becoming less granular and clearer and reduced in size, the nuclei appear large, distinct, and vesicular, changes suggesting those taking place in the atrophic tubules of the kidney in certain chronic forms of Bright's disease.

The islets of Langerhans are involved only secondarily and consecutively to the disintegration by the small amount of fibrous tissue ingrowth into the glandular acini.

The foregoing series of experiments represent the extremes of effects of a single irritant when acting intimately upon pancreatic

[1] See Oser, Die Erkrankhungen des Pancreas, Nothnagel's System, Wien, 1898, p. 339 et seq.

tissue; and it suggests that in human beings certain otherwise unexplained instances of chronic pancreatitis may be the remote results of acute destructive lesions of the pancreas having a certain grade of severity.

The rapid appearance of the lesions in the acutely fatal cases and the close relationship existing between parenchymatous degeneration and hemorrhage suggested studying the development of the lesions. This was done in the next series of experiments.

SERIES II. *Acid injections, with removal of portions of tissue at different intervals.* In order to determine the length of time required for the development of the lesions, injections of 1 per cent. HCl were made, usually into the ducts, and portions of the injected organ were, from time to time, excised. The procedures in this series were similar to the preceding, except that at the completion of the injection a solution of chloretone was introduced into the peritoneum. The sleep which quickly followed lasted throughout the duration of the experiment, at the end of which the animal was chloroformed. A purse-string suture was used for approximating the abdominal incision, and the animal was kept covered with cloths to keep up the normal body-heat during the experiment.

Experiment No. 11. January 17, 1901. Killed one hour and twenty minutes after injection consisting of 3 c.c. 1 per cent. HCl introduced intraparenchymatously. Site of injection swollen, congested, and beset with small hemorrhages. Other parts appear normal. (No chloretone used in this experiment.)

Urinary bladder contains urine; sugar positive by fermentation and Fehling's tests.

Experiment No. 14. Morphin, ether, and chloretone narcosis; 2 per cent. HCl solution injected into parenchyma of pancreas. Pieces removed as follows: After thirty-five minutes, seventy minutes, two hours and fifty minutes, and five and a half hours. Macroscopic hemorrhages were visible only at end of experiment.

The urine, after five and a half hours, contained sugar, demonstrable by copper and fermentation tests.

Experiment No. 15. Morphin, ether, and chloretone narcosis. Usual operation; 1 per cent. HCl into duct. Pieces were removed as follows: After one hour, at which time much edema and a few small punctiform hemorrhages; two hours, great swelling and edema

and streaks of hemorrhage; four hours, edema and increase in hemorrhages, the latter still of small area; eight hours, edema and larger irregular hemorrhages, and a few isolated points of hemorrhage in extremities in which injection had not penetrated immediately.

Fat necrosis already visible in peritoneal adipose tissue.

Much sugar in urine (copper and fermentation tests).

Histologic Examination. At the end of one hour (Experiment No. 14), after intraduct injections, the pancreas is already considerably affected. The first effect is, of course, the distention of the ducts with the injected fluid, but direct injury to the lining epithelium of the large ducts does not appear; from these the fluid flows backward into the smaller interacinous and intra-acinous ducts, which show generally a colloid material filling their lumina, although the epithelium still stains distinctly. From the ducts the fluid seems to pass very little directly into the acini themselves, but rather through the walls of the ducts into the pericanalicular and interlobular connective tissues. In these locations an albuminous and fibrinogenous fluid has exuded and undergone coagulation and precipitation. One of the striking effects is the wide-spread distention of the capillaries and the alteration in form of the red corpuscles. The interacinous capillaries and capillaries of the islands of Langerhans are turgidly swollen and the red blood-corpuscles are in *rouleaux*. Among these white cells are not especially abundant, but interacinous and intra-acinous microscopic hemorrhages have already taken place. The medium-sized interacinous veins show distention, red corpuscles in rouleaux, and *increase in polymorphonuclear cells.* The white cells, in occasional veins, form plugs, which do not, however, completely occlude the vessel, for an active emigration is going on. Leukocytes can be seen making their way through the walls and entering the adjacent tissues. Even red corpuscles can be seen engaged in the unruptured vessel walls, as well as just outside. There are no vascular thrombi. The parenchymatous cells already show distinct changes. Not many cells are affected, but occasional small islands of acinous cells are *partially or completely hyaline.* The nuclei are still stainable but weak, but the protoplasm is swollen and homogeneous; and *polymorphonuclear cells have begun to approach these areas or actually entered the altered protoplasm*; a few nuclear fragments are also visible. The largest hemorrhages, quite visible to the naked

eye in sections, are in the interlobular tissue and about the large veins, which latter show *leukocytic wandering and diapedesis through unruptured wall.*

Seventy minutes (Experiment No. 14) after intraparenchymatous injection the changes are considerably more marked than in the preceding specimen. The general engorgement is less striking and the hemorrhages, on account of the needle-puncture, not perhaps to be relied upon; but the degeneration of parenchymatous cells is far in advance of the other. The distribution of the degeneration is interesting as indicating the manner of diffusion of the injection. The hyaline cells are often the outermost layer next the interlobular connective tissue. Larger degenerated foci (consisting of one or more acini) are also present. Leukocytic emigration, as would be expected on account of the greater degree of degeneration, is a marked feature and gives rise to small islands among the necrotic cells. There are many leukocytes in the interstitial edema.

After eighty minutes (Experiment No. 11) this interstitial cellular accumulation begins to approach purulent infiltration.

At the end of two hours and fifty minutes (Experiment No. 14) the process has gained some in intensity. The hyaline foci have increased in size and in number. The cells have fused more or less, the nuclei are gone or very pale, leukocytes are wandering through the dead cells and showing greater numbers of fragmented nuclei. The interstitial hemorrhages are larger, and the hyaline material in the smaller ducts is denser.

A specimen taken four hours after the injection (Experiment No. 15) shows still further advance. The edema is extreme and has isolated certain lobules, the cells, however, still staining sharply; but the necroses are very large and numerous, and the nuclear changes are striking. In some areas only the very most central cells are entirely hyaline; the cells about are swollen and show granulation of protoplasm. The nuclei are also enlarged and less sharp of outline, and exhibit an unevenness and irregularity of dark blue staining in contrast to the sharp normal nuclear appearance (precipitation of chromatin substance). Smaller cells appear in the angles between the large degenerated ones, and show the same nuclear changes. Leukocytic infiltration is very marked, and white cells also begin to collect on the surface of the gland.

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After the lapse of five and a half hours (Experiment No. 14) the most important new phenomenon is the appearance of large numbers of large mononuclear cells in the interstitial tissue, chiefly about the veins, mingled with red corpuscles and polymorphonuclear cells. The mononuclears are very numerous. That they come from the veins is easily established by their position and the large numbers to be seen in sections of the vessels. The necrotic and degenerated cells begin to separate from one another, some assuming circular forms, and coincidently the leukocytic infiltration (chiefly polymorphonuclear and slightly mononuclear) is so greatly increased as to approach the appearance of an abscess. Parietal thrombi are to be made out in some medium-sized veins. Hemorrhage has increased considerably, and elevates the capsule of the gland.

The final specimens of this series are eight hours old (Experiment No. 15). They represent the pathologic process at its height, although the lesions are not as extensive as in many later specimens. But the number and distribution of the necrotic lesions, the degree of the cellular infiltration, and number, size, and position of the hemorrhages speak for great intensity of damage. To what has already been given there need only be added the coincidence of hyaline necroses and hemorrhage that may now be seen, and the free hemorrhages in other places causing complete disintegration of the acinous structures. The capsule of the gland is covered with a considerable fibrino-purulent hemorrhagic pseudomembrane. The large pancreatic duct in the section shows injury. The epithelium is hyaline and desquamated, and the wall infiltrated with leukocytes. Hemorrhage has also taken place into the duct.

The peritoneal fat necroses are typical, and about them a well-advanced cellular accumulation may be noted. While there is no record of fat necroses occurring so quickly as in this instance, we have little doubt but that they may make their appearance even earlier than eight hours after injury to the pancreas. Especial attention has not been directed to the elucidation of this question.

This series of experiments has a general as well as special interest. The rapidity with which morphologic changes in cells may be made out and the celerity with which emigrative phenomena in vessels takes place in warm-blooded animals is well illustrated by these examples. That degenerative, inflammatory, and hemorrhagic lesions

are correlated in the pancreas may now be considered as demonstrated. There need be no time interval, or no considerable one, between the appearance of the several phenomena. To decide upon the effects of hemorrhage upon the pancreas, in the absence of other lesions, the next experiments must be consulted.

SERIES III. *Injection of defibrinated blood.* In order to determine the effects of sterile blood upon the pancreas injections of defibrinated blood were made. It will be recalled that great differences of opinion have existed among writers upon pancreatitis and pancreatitic hemorrhage in human beings as to the precedence and succession of hemorrhage and inflammation. Hitherto no effort has been made to test the matter experimentally in the absence of the use of some foreign irritating substance.

Experiment No. 16. Twenty c.c. of defibrinated dog's blood (obtained from second animal just before injection) injected into the duct of Wirsung. Dog succumbed thirty minutes after injection. Death attributed to anesthetic. *Urine contained sugar* by Fehling's tests.

Experiment No. 17. Injected, May 30th, 10 A.M., 10 c.c. defibrinated blood into pancreatic duct. Dog quickly recovered from effects of operation. Chloroformed June 4th, 11 A.M.

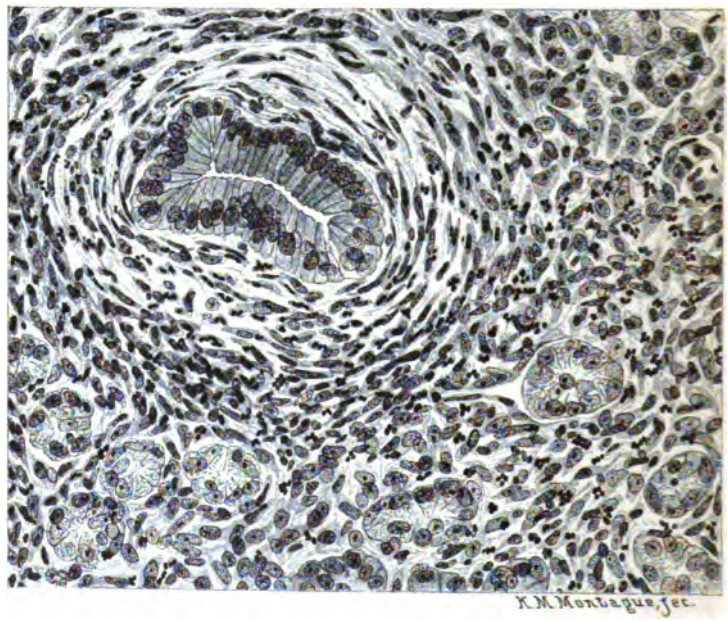
Autopsy. No fluid in peritoneum; serous membrane bright. In the mass of fat beneath ensiform cartilage several small necroses, surrounded by a zone of hemorrhage. The perirenal, peripancreatic, and omental fat show necroses.

The pancreas, extending from the splenic extremity to the descending duodenal portion (site of blood injection), presents a reddish-brown and mottled appearance and great increase in consistence. The descending portion, within the omentum, appears normal.

Experiment No. 19. June 14, 1901, 10 A.M. Same experiment, except that the defibrinated blood was injected into the parenchyma. Chloroformed June 16th, 10.30 A.M. Middle portion of pancreas, in which one injection was made, appears firmer than normal. A few fat necroses. Otherwise the peritoneal cavity and organs are in normal condition.

Experiment No. 20. June 24th, 10 A.M. Sixteen c.c. defibrinated blood from same dog injected into pancreatic duct. Chloroformed June 27th, 10 A.M. The dependent portions of peritoneum contain

PLATE III.



EXPERIMENT No. 20. Intra-acinar and peri-canalicular sclerosis of pancreas following injection of defibrinated blood into the duct of Wirsung Polymorphonuclear leukocytes and fibroblasts are seen destroying the normal glandular arrangement.

a small amount of cloudy fluid, and the liver is covered by a thin film of fibrin. The intestinal wound has suppurated, and the adjacent portion of the pancreas is involved in the purulent infiltration. The pancreas is faintly mottled with reddish-brown areas of discoloration and the mid-portion (injected area) is firmer than normal. Duodenal and splenic ends appear normal.

Cover-slips from the area of suppuration showed cocci and colon-like bacilli. Urine free from sugar.

Histologic Examination. Experiment No. 16 is useful only to demonstrate the penetration of the injection. The duodenal end escapes injection from the duct of Wirsung. The mid-portion is easily and the splenic end less easily injected. The blood passes through the larger ducts into the acini and is distributed in spaces between the columns of cells. The corpuscles can be traced to the islets of Langerhans, which they often surround *and not infrequently enter*, distributing themselves between the columns of cells. The blood also passes into the large connective tissue septa. Injected into the parenchyma the distribution is far less general.

On the third day the blood has disappeared from the parenchyma (Experiment No. 20). The organ has not returned to the normal, for in those parts in which the blood penetrated new tissue is developing. It is not a general new growth, but affects lobules or groups of lobules. Nor is the growth about the lobule; it is intralobular and intra-acinous. The new growth takes place from several centers, apparently in the main from the ends of the fine interlobular strands of connective tissue; but the investment of the medium-sized ducts also supply the beginning. It first appears in the form of young cells with vesicular nuclei, among which a small number of irregular polymorphonuclear cells occur. At first sight the appearance may be taken for new islets of Langerhans, but it is soon apparent that the areas are more irregular, have a different distribution, and are composed of different cells. Even at this time occasional lobules have been largely substituted by a cellular connective tissue in which many fibers are already to be seen. Another twenty-four hours, and the new tissue has progressed considerably.

Specimens which have been allowed to remain five days (Experiment No. 17) show great advance. Whole lobules are extensively destroyed, islands only of glandular cells remaining. The new

tissue is young, cellular, but already showing fibers. Along the finer interlobular strands linear masses of small fibroblasts appear.

The islands of Langerhans suffer extensively and early. When the process is advanced—say on the fifth day—they are no longer distinguishable among the fibrous growth.

The main ducts and main septa of connective tissue are little altered.

When the injection has been made into the parenchyma (Experiment No. 19) the effect is less marked and quite different. After forty-eight hours the main septa still show the presence of the blood in colored and decolorized corpuscles; they are smaller, and new cells—fibroblasts presumably—are appearing among the fibers and about the large vessels.

The fat necroses are typical. Those five days old show advanced proliferative substitution.[1]

The injection of defibrinated blood into the duct of Wirsung and its penetration into the interstices of the parenchyma of the pancreas do not suffice to set up acute pancreatitis. Such injections are quickly followed by decolorization and disappearance of the corpuscles from the organ and the occurrence of proliferative activity of the connective tissues about and within the acini. This proliferative process quickly gives rise to a new growth of tissue which takes the place of the glandular acini and islands of Langerhans. The precise mechanism of this process has still to be worked out. The process of substitution does not affect the whole organ, as the blood does not enter the descending duodenal extremity of the pancreas. Nor does the entire mid-portion or tail of the pancreas undergo sclerosis. As far as it has been followed the process is nodular, affecting islands of tissue somewhat separated by more normal structure. A later report will be made upon some of the undetermined aspects of the subject.

Upon what constituent of the blood these effects depend remains to be determined. The next experiment may serve to answer this question.

SERIES IV. *Injection of blood-serum. Experiment No.* 23. July 12th, 10 A.M., 5 c.c. of blood-serum, obtained from same femoral

[1] Flexner. Journal of Experimental Medicine, No. 4, vol. ii. p. 413.

artery of dog one hour before, injected into duct of Wirsung. Edema over mid-portion of pancreas. Chloroformed July 16th, 12 M. Pancreas appears normal. No fat necrosis; no sugar in the urine by Fehling's test.

Histologic Examination. Pieces of the pancreas taken from the duodenal, splenic, and middle portions showed no alterations. The parenchyma and interstitial tissues were of normal appearance and dimensions.

SERIES V. *Splenectomized dogs. Injection of acid.* Katz and Winkler[1] noted in their experiments for producing fat necroses in dogs that the spleen was small and firm. Bearing in mind Schiff's[2] and Herzen's[3] experiments on the influence of the spleen upon the production of the tryptic ferment of the pancreas, they conceived that a similar connection might exist with the fat-splitting enzyme. They extirpated the spleen of several dogs and a few days later constricted the pancreas with ligatures, between which incisions into the organs were carried. Fat necroses were noted only to a slight degree, whence Katz and Winkler conclude that in the development of pathologic conditions an interaction very probably exists between the spleen and the pancreas. That the spleen is not essential to the occurrence of pancreatitis and consequent fat necrosis the following experiments tend to prove:

Experiment No. 7. January 4th, 3 P.M. Splenectomized dog by tying off the bloodvessels proceeding to and from the spleen, and removing that organ. After this usual operation with injection into pancreatic duct of 1 per cent. HCl solution. Dog died during the night. Autopsy January 5th. Pancreas greatly swollen and hemorrhagic. Bloody fluid in peritoneal cavity. *Fat necrosis in peritoneal fat about ensiform cartilage and in the omental and mesenteric fat.*

Experiment No. 8. January 4th, 4 P.M. Same as Experiment No. 7. Dog died during night. Pancreas little altered; a few hemorrhagic areas in the substance. Bloody fluid in the peritoneum. *Necroses present in peritoneal fat.*

The previous experiments show that in recently splenectomized

[1] Archiv f. Verdauungskrankheiten, 1898, Bd. iv. p. 289.
[2] Schweiz. Zeitschr. f. Heilkunde, 1862, p. 201.
[3] Pflüger's Archiv, Bd. xxx. p. 295, and Bd. lxxxiv. p. 126.

dogs injury inflicted upon the pancreas is able to cause pancreatitis and fat necrosis. Assuming the view expressed by Katz and Winkler to be improbable, it is not disproved by the two experiments related in that the time relation between removal of the spleen and injury to the pancreas is so close that it is easily possible for the hypothetical substance elaborated by the spleen to be still present in sufficient amounts to act upon the pancreatic cells. To obviate this factor other experiments were performed.

Experiment No. 9. January 8th, 2 P.M., dog splenectomized. The animal quickly recovered from the operation; no ill effects noted from absence of spleen. January 17th, 2 P.M., usual operation; injected 12 c.c. 1 per cent. HCl into pancreatic duct. Dead January 18th, about 6 o'clock. The entire pancreas, except the extreme duodenal end, is dark red in color and much swollen. *Fat necroses are present in fat beneath the abdominal wound, in the omental and mesenteric fat.*

Experiment No. 10. January 8th, 3 P.M., dog splenectomized. Second operation January 17th, 3 P.M. Injected 12 c.c. 1 per cent. HCl into duct of Wirsung. Death January 18th, 12 M. Pancreas intensely hemorrhagic and much swollen. *Fat necrosis present in peritoneal fats in several parts.* The urine shows presence of sugar to Fehling's and fermentation tests. The hemorrhagic portion of the pancreas has been invaded by gas-producing bacilli, which have caused small gas-blebs to appear over the surface. Films prepared from this part show bacilli having the morphology of B. aerogenes capsulatus.

These experiments, and especially the last two, may be taken as excluding the spleen from any necessary participation in the functions of the pancreas associated with the production of the fat-splitting ferment in so far as the liberation of the steapsin is required for the causation of fat necrosis.

Histologic Examination. There is nothing exceptional in these specimens. They show typical lesions of severe grade in the pancreas, and pancreatic and parapancreatic fat necrosis of typical structure.

SERIES VI. *Injection of bile. Experiment No.* 21. June 24th, 11 A.M., injected 6 c.c. bile taken from gall-bladder of same animal into duct of Wirsung of dog. Immediate edema and bile-staining

of middle and splenic end of organ. Animal found dead 8 A.M. June 25th; partial decomposition. The middle portion of the pancreas is dark in color and apparently hemorrhagic; the splenic end is dark, reddish-brown in color, and the duodenal end somewhat swollen. Emphysematous blebs are present within the dark portions of the organ. Fat necroses are numerous in the peritoneal fat. The abdominal cavity contains about 100 c.c. of blood-stained fluid.

Experiment No. 22. July 1st, 10 A.M., 4 c.c. of bile from same dog injected into duct of Wirsung. Immediate slight staining of mid-portion of organ. Animal found dead July 2d, 9 A.M. Weather very warm and decomposition advanced. The splenic extremity and middle portion of the pancreas are firm and mottled gray and red. Many fat necroses in the peritoneal fat.

Histologic Examination. The lesions are typical of hemorrhagic pancreatitis and fat necrosis. In the extent and distribution of the focal hyaline necroses of pancreatic cells, and especially in the extent of hemorrhage, these specimens are behind those of equally acute development produced by HCl injections. On the other hand, the character of the lesions is identical, and the inflammatory vascular reaction pronounced. The bile has become indistinguishable among the other constituents.

Glycosuria. A few words will suffice in dealing with this condition. It was, as the protocols exhibit, a regular attendant of the operative procedures upon the pancreas. The rapidity of its occurrence was a matter of some surprise. The earliest times at which tests were made were thirty and eighty minutes after defibrinated blood and intraparenchymatous injection of 1 per cent. HCl (Experiments Nos. 11 and 16 respectively) and sugar were found in the urines. From those periods on it was commonly found in animals succumbing to acute lesions of the pancreas. The percentages of sugar were not estimated. If the injury do not prove fatal within twenty-four to seventy-two hours the animals usually survive to develop chronic inflammations, cysts, and abscesses of the pancreas, to which they do not usually succumb. In such animals the sugar persists for some days (Experiment No. 5, present on fifth day, but not at end of three weeks when chloroformed) and then disappears.[1]

[1] See protocols, previous paper, op. cit., p. 752 et seq.

The glycosuria in all these cases is to be looked upon as the result of direct insult inflicted upon the pancreas and similar to other operative glycosurias. On account of the peculiar relation which the pancreas holds to the carbohydrate metabolism, traumatic glycosuria probably attends more regularly and develops more quickly upon injury to this viscus than to other organs of the body. Experiments to determine the ultimate fate of animals developing chronic pancreatic lesions have thus far not been made. The longest survivals which have been permitted by us do not exceed four or five weeks.

Conclusions.

1. Pancreatitis follows upon a variety of insults to the pancreas, and is capable of developing with great rapidity. The introduction of such a foreign body as artificial gastric juice into the pancreas gives rise to degeneration, hemorrhage, and emigration of leukocytes within the brief space of one to two hours.

2. Chronic pancreatitis may represent the remote result of acute destructive lesions of the pancreas having a certain grade of severity.

3. Perversion of normal secretions whereby they enter the pancreas, as illustrated by the effects of gastric juice and bile, are efficient causes of pancreatitis, associated with hemorrhage and fat necrosis.

4. The presence of blood alone in the tissues of the pancreas does not set up an acute inflammation; the tendency is for the rapid production of a chronic proliferative interacinar and intra-acinar pancreatitis.

5. The effects of blood are not produced by blood-serum separated from the corpuscular elements.

6. The spleen has no influence upon the development of pancreatitis and the production of fat necrosis.

7. Fat necroses attend all forms of pancreatitis, and are more numerous and wide-spread the more acutely the pancreatic lesions develop. They may appear as early as eight hours following injury to the pancreas.

8. Glycosuria appears quickly after injury to the pancreas; it may persist for several days and then disappear, although the pancreas has suffered permanent partial injury.

LITHEMIC OR RECURRENT CORYZA.

By B. K. RACHFORD, M.D.,
of Cincinnati, Ohio.

An attack of lithemic coryza is sudden in its onset, and is characterized by intense photophobia and hypersecretion from the eyes and nose. The profuse watery discharge from the nose irritates and causes a redness and swelling of the lip, over which it is discharged. The tears overflow in abundance, and the eyes are red and swollen. Accompanying this, the patient is in a state of extreme nervous irritability and has some elevation of temperature. These symptoms continue for two or three days and then disappear as rapidly as they came. The child within a few days is quite well, and may continue so for a variable length of time, when, without apparent exciting cause, a similar attack recurs.

In illustration of this symptom-group I present the following case:

A girl, nine years of age, whose father for many years suffered from migraine; her mother died from diphtheria when she was but a few weeks old, and since that time the child has been under the care of a painstaking and intelligent grandmother. The previous history of this patient contains no serious illness; there is, however, a history that she has always been nervous and subject to light bilious attacks characterized by nausea and vomiting. From the grandmother I learned that the child, when six years of age, commenced to have attacks of intense irritation of the mucous membranes of the nose and eyes, from which she has suffered at intervals ever since. My first acquaintance with this patient was made during one of these attacks, in January, 1899. I found her in a darkened room, suffering so intensely from photophobia that I could not let sufficient light into the room to make a satisfactory examination. The child was in a state of extreme nervous irritability, which added to the difficulty of inspecting the case. I managed to see, however, that the eyes were swollen, that the nostrils were intensely irritated, and that an abundant watery secretion was running from both eyes and nose, producing considerable irritation of the lip and other parts over which it ran. I desisted from further examination to obtain from the grand-

mother something more definite concerning the child's medical history. I learned that she had been taken suddenly ill with this attack about noon of the previous day. She at once complained of the photophobia and nasal irritation and went to bed in a darkened room, where she had remained up to the time of my visit at 5 P.M. The symptoms at this time, thirty hours after their onset, had not abated the least in severity. I learned also that the many similar attacks from which my patient had suffered lasted on the average two or three days, at the expiration of which time she would get well as quickly as she became ill. All pain, irritation and hypersecretion from the eyes and nose would rapidly subside, so that within a few days the child would be at school again, apparently as well as before the attack. In the intervals between these attacks there was no trouble with the eyes or nose, and, apart from being a nervous child suffering somewhat from constipation, she was not considered ill. She was quite equal to all the outdoor exercise incident to childish play, and went through her school work as easily as the average child. Of late these attacks had been more frequent and more severe, occurring at intervals of two or three weeks. As a rule, however, there had been in the past a longer interval than this between these attacks, and at times, especially in the summer, she had gone for several months without having one.

This very clear history of self-limited paroxysms of coryza, recurring in a young patient having a family history of migraine, placed me at ease concerning my patient's present condition. I felt assured that lithemic poisons acting through the vasomotor nerves of the part affected were responsible for the symptoms, and that these would spontaneously disappear as they had done in many previous attacks. I promised, however, to return that I might talk over with the grandmother a plan of treatment looking to the prevention of these attacks. Two days later I found the child playing about the room in an almost normal condition, and I very much questioned whether the potassium bromid and belladonna, which I prescribed at my first visit, had anything to do with shortening the attack. I now advised that the child should have as much exercise as possible in the open air, that she should avoid tea, coffee, sweets, and an excess of red meats, that she should drink milk and eat cereals, vegetables, fruits, chicken, fish, eggs, and once or twice a week a piece of red meat. Her bowels were to be kept open with a mixture containing sodium sulphate, sodium phosphate, and lithium benzoate; a dose of this medicine, sufficient for the purpose, was to be taken every morning before breakfast. Three weeks later this child had a very slight attack, not severe enough, however, to put her in bed, and lasting less than twenty-four hours. From that time to the present, nearly two years, she has been kept under observation, and during the whole of this period she has not had a severe attack of coryza. A number of times she has been "threatened" with an attack, but in every instance the premonitory symptoms disappeared and the attack was aborted. She has had a number of slight "bilious attacks" (recurrent vomiting) during the past two years. In the last one of these attacks (November, 1900) the nausea and vomiting lasted twenty-four hours,

and there was at the same time a little irritation of the nose and eyes. The history of this patient is completed with the note that the urine passed during the severe attack of lithemic coryza, in which I first saw her, was scanty, highly colored, strongly acid in reaction, had a specific gravity of 1030, and contained an excess of the alloxuric bodies.

Cases of this character, rather less severe than the one I have just described, are not uncommonly seen in lithemic children, and this symptom-group may alternate or commingle with other symptom-groups of lithemia. There seems every clinical reason to believe that these cases are produced by lithemic poisons acting, as these poisons are accustomed to act, through the vasomotor nerves, and the brilliant results which follow the antilithemic treatment of these cases must for the time being justify their inclusion under the general heading of lithemia.

Pediatrists have given little or no attention to these cases; they are, however, described by laryngologists under the title "vasomotor coryza" and "periodic hyperesthetic rhinitis." Lenox Brown[1] speaks of these cases as being caused by "sensitive spots in the nose, with a vasomotor debility and some local irritant as co-operative factors." Kyle[2] says that "they may be due to a local irritant acting from without, usually of botanical origin, or to local irritation from an internal irritant, such as uric acid. . . . . The form due to the rheumatic or gouty diathesis is more amenable to treatment than any of the other varieties." And for these cases he prescribes water, sodium phosphate, lithium, and "Basham's mixture."

Jules Comby classes among the respiratory manifestations of lithemia in childhood, "spasmodic coryza, sibilant bronchitis, and asthmatic attack." The close relationship of these symptoms is evident, and it is also clear that the same poisons, acting through different parts of the pulmonary vasomotor system, may produce either coryza or asthma. Haig and many other writers, among them the author of this paper, have expressed the opinion that the uric acid diathesis is a strong etiological factor in producing certain cases of asthma in the adult. My own experience, however, leads me to believe that well-developed lithemic asthma is a comparatively rare condition in childhood, but that lithemic coryza is not an uncommon symptom-group.

[1] The Throat and Nose and their Diseases, 1899.
[2] Diseases of Nose and Throat, 1899,

A CASE OF SUBCORTICAL GLIOMA OF THE LOWER PART OF THE LEFT ASCENDING FRONTAL CONVOLUTION SUCCESSFULLY REMOVED.

A Contribution to the Nature of the Speech Disturbance Arising from Lesions in this Situation.

By JAMES STEWART, M.D.,
OF MONTREAL, CANADA.

L. P., aged thirty-seven years, a painter, first came under observation on December 6, 1900. His complaints were of temporary attacks of complete loss of speech. He was, with the exception of occasional slight frontal headaches, as far as he could judge, in perfect health up to August 2, 1900, when he was suddenly seized with an attack solely characterized by absolute loss of speech, being unable to utter a word or sound of any kind—a condition of perfect mutism. This state lasted about thirty minutes. It was not attended or followed by other symptoms of any kind. About the middle of September, or six weeks later, he had a precisely similar attack, lasting about the same length of time. Up to the time of his admission he had in all ten such seizures, the last one occurring on the morning of his admission to the hospital. He arrived at the railway station, and after getting into a cab he was unable to direct the cabman where to drive him. Like the previous attacks, it passed off in the course of about half an hour. During the attacks he understood perfectly what was said to him, and knew what he desired to utter. He was frequently tested whether he was able to read and write during the attacks, and is confident that he was able to accomplish both acts as well as he ever could.

He was not then nor at any time previously troubled with either nausea, vomiting, or headache.

During the last few attacks he has felt a sensation of numbness or deadness in the index and middle fingers of the right hand. It is a very slight sensation and does not last as long as the loss of speech. It is not felt until after the latter sets in, and disappears before it. At no period has there been any muscular weakness during or after the periods of loss of speech, neither has he observed double vision.

He has always been healthy and regular in his habits. There is no history of syphilis.

His father died at sixty years of age from heart disease; his mother is living and in good health. There is no family tendency to malignant disease, to tuberculosis, or to rheumatism; there is no neurotic family history.

His condition on admission on December 6, 1900. He is a well-nourished man, aged thirty-seven years, of medium stature, active in all his movements. He is fairly well educated and possessed of good intelligence; he sleeps well.

Nervous System. During the two days that he spent in the hospital at this time there was no recurrence of the attacks of mutism. Dr. Birkett made a very careful examination of the larynx, and found no disturbance of either the abductors or adductors. Both were found to move freely on phonation.

All the functions of the central nervous system were normal. There was no motor or sensory disturbance of any part.

A careful examination into the different forms of the muscular sense did not elicit any signs of abnormality. The organic reflexes of swallowing, defecation and micturition were not in any way interfered with. The knee-jerks were found slightly exaggerated, and all the superficial reflexes except the pharyngeal were present.

Examination of the eyes did not reveal any deviation from the normal in either the external or internal muscles, nor in the optic nerve.

The urine was free from albumin and sugar, as well as found normal in other respects.

A careful examination of the remaining organs and systems failed to reveal any signs or symptoms of disease.

He was discharged at his own urgent request after remaining in the hospital for forty-eight hours.

It was thought likely that the condition was one of functional (hysteric) mutism. The loss of the pharyngeal reflex, in addition to the intermittent mutism, were looked upon as a combination of symptoms that were more likely due to the functional than organic disturbance. Had more consideration been given to the slight but still clearly defined sensation of numbness accompanying the more recent attacks, this error would have been avoided.

Condition since his discharge from the hospital and his re-admission on January 24, 1901. Three days subsequent to his discharge another attack of "speechlessness" similar in its character and duration to the previous attacks, was experienced by him, and up to a week before his re-admission similar attacks were frequent. For a week previous to his re-admission he had no disturbance of speech. He was quite clear mentally during the attack, knowing well what words he would like to say, but was unable to utter them.

On January 3d he had "an attack of spasmodic jerking of the muscles over the right lower jaw," lasting a few seconds. At the same time he felt a numbness and weakness in the right arm. These symptoms, he says, have lasted, although in a much diminished degree, up to the present. Several minor attacks of spasm of the muscles of the lower part of the face have recurred, but all less marked than the initial one of January 3d. The numbness he refers mainly to the hand and forearm. It is always more marked during the morning hours. There is no subjective disturbance of sensation in the right lower limb.

He complained of his sight failing, but was still able to read fine reading

type. During the attack of facial spasm on January 3d he was blind for a few seconds in the right eye. From January 1st and up to his re-admission headache, both frontal and vertical, has been often present. Frequently it is so severe at night that he has been unable to sleep. Vomiting has been present at rare intervals.

Condition on January 25th, the day after his re-admission. Nervous Symptoms. His mental state is in every respect normal.

Speech. There is a very definite dysarthria, words beginning with v, g, k, s, b, p, w are pronounced with difficulty. At times he has trouble in recalling certain words, but this disability is on some days not present and was not at any period an obtrusive symptom. It might with truth be said to be only a slightly exaggerated condition of a not infrequent normal state.

He had no difficulty in understanding what was said to him. At this period he was able to write and read both printed and written sentences. He recognized objects of various kinds quickly and named them correctly, although more or less imperfectly from the disability of articulation. His gestures were found to be correct. There was an appreciable difference between the strength of the muscles of both the upper and lower extremities, those on the right being weaker than those on the left. In the case of the lower limbs the difference was not more than barely appreciable. He, however, maintained that he was distinctly conscious of a weakness in the limbs on the right side. He complained of a more or less constant sensation of deadness or numbness in the right forearm and hand, and occasionally of a similar sensation in the left forearm and hand. There was no objective disturbance of sensation in the extremities or elsewhere.

Eyes. Dr. Buller found a well-marked double optic neuritis. This condition was about equally present in each eye. The pupils were medium sized, equal, and reacted normally to both light and accommodation. There was no diplopia or other evidence of ocular paralysis.

Facial Nerve. Two pronounced and distinctive symptoms, pointing to disturbance of the cortical origin of the right facial, were found present, and both persisted. They were: 1. An intermittent, clonic spasm of the muscles of the lower part of the right side of the face. The spasms occurred several times a day, and sometimes an interval of two or three days elapsed between them. They lasted from a few seconds to a few minutes, and drew the right angle of the mouth outward, and at times slightly upward. 2. There was a weakness of the muscles of the lower part of the right face, the angle of the mouth on this side being lower and the nasolabial fold wellnigh obliterated. On voluntary movement of the two sides of the face the difference in strength of the corresponding muscles was very striking. The difference between the two sides was more pronounced from voluntary than from emotional movement.

The Hypoglossal Nerve. On his re-admission it was observed that the tongue was protruded to a slight extent to the right side; as this condition subsequently increased, it was noticed that after each facial spasm there was an increase of the weakness of the right half of the tongue. When the tongue

was protruded, and even when at rest in the mouth, its right half was the seat of tremor. After each attack of spasm of the facial muscles the paralysis was more evident than formerly. After a period of freedom from spasm the muscles would regain to a slight extent the power lost, but as a rule there was always superadded to the weakness a further degree of disability after each facial spasm.

The other cranial nerves did not show any evidence of either cortical or peripheral disturbance.

Reflexes. Both knee-jerks were slightly exaggerated, the right being a little more so than the left.

All the superficial reflexes were normal. There was no interference with the organic reflexes. There was no evidence of disturbance of function elsewhere than in the nervous system; the temperature, respiration, and pulse remaining normal.

There was tenderness on percussion, and a persistent increase of temperature of $\frac{3}{8}$° F. over the left side of the skull.

Course of events up to the day of operation, March 9, 1901. *Spasms.* The spasms of the muscles of the lower part of the right face continued to recur at irregular intervals. There were rarely more than one or two spasms in any one day. Sometimes an interval of three or four days elapsed between them. Their duration and extent did not differ in any essential degree from those already described.

Paralytic Phenomena. The paralysis of the lower branches of the right facial nerve and of the right half of the tongue continue to increase in depth. It was always observable that both paralytic states were worse after an attack of spasm. The transient weakness of the right hand and arm, previously observed as occurring after attacks of facial spasm, is less pronounced. The dynamometer shows, in fact, that the power in the right is greater than in the left hand. It is about equal to what one would expect it to be in a normal state. It is, however, different in the right hand from a normal grasp. It is a short, sudden exertion which is not maintained, differing in this respect also from the well-maintained grasp of the left hand.

Sensory Disturbance. The only symptoms of a sensory character were entirely subjective, with the exception to be mentioned, and confined to the right hand and the right half of the tongue and the lower part of the right face. Now and then he would say that he felt some numbness in the left forearm and hand.

The only ascertainable objective disturbance of sensation was in the right half of the tongue, where there was a very obvious difference between the right and left halves to the sense of touch, while painful and thermic stimuli appeared to be normal.

Tactile sensation as well as painful and thermic stimuli were elsewhere normal. He quickly recognizes when his face or tongue is touched simultaneously by either two sharp or dull points. The acuteness of this form of sensation appears to be normal, not only in the right face and tongue, but also in the extremities.

Muscular Sense. He readily recognized any and every position in which his right extremities were placed. If the left extremities were placed in a certain position he could without difficulty place the right extremities in the same position when his eyes were closed. He is perfectly able to name common domestic articles by the sense of feeling; he estimates also fairly accurately the weight and shape of objects when placed in either the right or left hand.

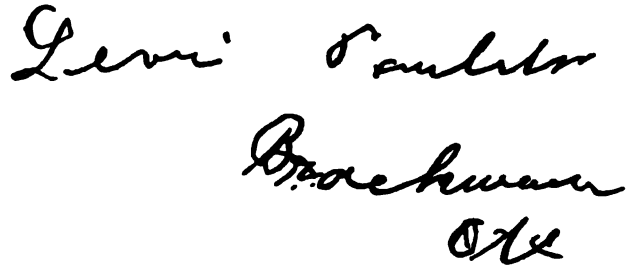
Speech Disturbance. The chief if not the only disturbance in speech was in articulation. There was from the time of his entrance into the hospital a gradual progressive deterioration of the power of articulation from slight dysarthria up to a practically complete anarthria. The labials, b, p, m, were from the first pronounced with difficulty. Finally he was unable to articulate any one letter of the alphabet that could be understood with the exception perhaps of the letter o. The simplest words were so imperfectly articulated that it was impossible to understand him. He, however, in spite of his failure to convey his meaning, made persistent efforts at speaking. He evidently understood the words he wished to express, and appeared to have no difficulty whatever in calling them up in his memory; he knew, for instance, the number of letters or syllables in a word. There was the same difficulty in naming the numerals as in pronouncing letters or words.

Now and then it was noticeable that he had difficulty in recalling certain names, but this was at no time a pronounced symptom. For several consecutive minutes he would make persevering attempts to speak, seemingly always calling up the proper word without difficulty, but he was not understood because of the defect in articulation.

At no time was there any evidence of word deafness or of word or object blindness. He was able to read, and he spent the greater part of his time in doing so when the headache lessened.

Defect in Writing. He was able to write words of one syllable without making any mistakes, but even a very simple word required an effort on his part. Words of two or more syllables were very rarely written correctly. He made a fair success with the first syllable, but stumbled over the second. When asked to write his own name and place of residence, he was unable to do so correctly except the first syllables. The following is the results of one of the most successful of his efforts:

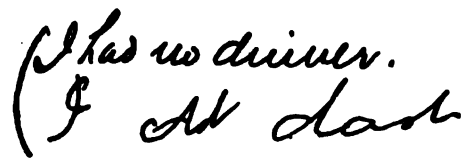
To write—Levi Poulin, Brockville, Ont.



His success in copying printed or written words was no better than his attempts at spontaneous writing, as the following example will show. When asked to copy the word hospital in large print the result was:

HOSPITAL.

When asked to copy the following words:
"I had no dinner," he wrote:



The defect in writing was more a dysgraphia than an agraphia.

Electric Reactions. The reaction of the paralyzed muscles supplied by the right facial nerve were normal to faradism.

Vision. The vision was slowly lessening, this corresponding to an increase of the optic neuritis which was now especially marked on the left side. (Dr. Buller's report.)

Headache. During the last month previous to operation the headache was more or less continuous and severe, being especially so during the night. It was chiefly vertical, and often extended down the left side of the head to the left shoulder and down the left arm.

Laryngeal Muscles. Repeated examinations of the larynx were made by Dr. Birkett during the patient's stay in the hospital. At no time was he able to detect any deviation from the normal.

Both the abductors and the adductors were found to be capable of normal action. An examination was also conducted by Dr. Birkett just after the patient was put under ether and before the operation was proceeded with, with similar results.

The diagnosis of an intracranial tumor was made on the following grounds: 1. The constant severe headache having no other discernible cause.

2. The bilateral optic neuritis.

3. The vertigo.

4. The exaggerated knee-jerks and ankle-clonus.

It was localized on the left side of the brain at the lower part of the ascending frontal convolution, because the dominant symptoms were:

1. Spasms of the muscles of the lower part of the right side of the face.

2. The presence of an abiding weakness of the muscles of the lower part of the right side of the face.

3. A paresis of the muscles of the right side of the tongue.

4. The presence at times of a slight paresis of the right arm and hand, together with disturbed subjective sensation in the same parts, showing that the centers for these, although not seriously interfered with, were, however, in the immediate neighborhood of an irritating lesion.

Further, it was considered to be subcortical on account of—

1. The practical absence of aphasia.

2. The presence of a dysarthria going on by slow degrees to an almost complete anarthria.

That it was, however, not far from the cortex was shown by—

1. The spasms of the muscles of the lower part of the right side of the face. To induce these spasms it was rational to suppose the presence of a lesion in the immediate neighborhood of the cortical centers for the lower facial muscles.

2. A unilateral lesion to induce a dysarthria must be sufficiently near the cortex to include not only the speech tracts, which pass down the same side, but also those that cross over in the corpus callosum and pass down the opposite side of the brain.

The Nature of the Growth. The nature of the growth could not from the symptoms or course be determined.

A glioma was suspected because of the age of the patient and the failure of active antisyphilitic treatment over a period of six weeks, to influence in any way favorably the disease.

A tuberculous tumor was not likely, because of the age of the patient, his general good nutrition and the absence of tuberculosis elsewhere, and, further, there was no family history pointing to tuberculosis.

Operation performed by Dr. James Bell, Professor of Clinical Surgery, McGill University, on March 9, 1901. On account of its greater safety ether was used instead of chloroform for inducing anesthesia. The situation of the fissure of Rolando being mapped on the shaven scalp, an ovoid flap, two inches in its transverse and two and a half inches in its vertical measurement, having the fissure of Rolando slightly posterior to a line drawn down obliquely through the center, was raised upward.

The dura mater was incised about a quarter of an inch from the edge of the bone incision and everted upward. The brain was pulsating, and the pia mater slightly cloudy. The cortex appeared to be normal, but on palpation a hard, resistant mass was felt in the brain substance, at the lower and more anterior part of the opening. The brain substance over this mass was incised to the depth of a quarter of an inch, the finger introduced, and a hard, irregular tumor was enucleated and removed.

This tumor mass was about an inch in its longest diameter, and from one-half to three-quarters of an inch in its shortest diameter. It was encapsuled and was of firm consistency and of a whitish color.

On removing the tumor about two ounces of turbid, watery fluid escaped from beneath it, leaving a cavity just over the first part of the horizontal arm of the Sylvian fissure.

There was considerable bleeding from the vessels of the pia mater, which was ultimately stopped by ligature.

A glass tube was inserted into the cavity and brought out through a small trephine opening at the line of incision through the bone. The dura mater was closed by sutures of catgut and the osteoplastic flap placed and held in position by sutures through the skin.

He rallied well after the operation.

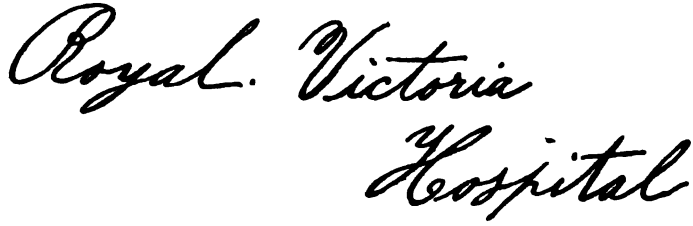
Chief noteworthy events after the operation. Speech. His articulation for several days after the operation was, if possible, worse than before. It was very instructive to notice how the march of improvement, when it began about the eighth or ninth day after the operation, progressed.

He was first able, with a fair degree of distinctness, to pronounce simple words of one syllable, but it was not until about the third week that he was able to articulate words of two or more syllables. When he left the hospital, twenty-eight days after the operation, his articulation was nearly normal; he, however, spoke slowly, and words of more than one syllable required a distinct effort. The labials especially called for a deliberate effort.

There was no difficulty manifested after the operation in calling up the names of objects or persons. He understood readily and perfectly all spoken and written commands, and was able at once to recognize all objects and to name them correctly.

Writing. About the same time that the speech showed signs of improving his writing also distinctly improved, and by the time he left the hospital he could readily write correctly words of several syllables. The improvement in writing was first noticed in words of one syllable, and a few days afterward in words of two or more syllables.

The following is from a letter written by him two weeks after his return home and six weeks after the operation.



The contrast between this and the efforts he made before the operation to write his own name and place of residence is very great and most interesting.

Spasms. During the two or three days subsequent to the operation the spasms of the muscles of the lower part of the right side of the face were more frequent than formerly, but after this date they gradually subsided, and after the tenth day they ceased, and have not since returned.

The Faciolingual Paralysis. The day following the operation the facial paralysis as well as that of the right half of the tongue were more marked

than previously. Twelve days afterward the tongue was protruded in a straight line, and the facial paralysis was not evident when the muscles were at rest. When he left the hospital on the twenty-eighth day after the operation there was no trace of either facial or lingual paralysis.

Sensory Disturbance. The sensory disturbances, like those of motion and speech, were more marked for a few days succeeding the operation, but they afterward entirely disappeared. The headache gradually lessened, and about the end of the first week was no longer felt.

Dr. Buller, on the twenty-seventh day after the operation, examined the eyes, but was not able to satisfy himself that there was an appreciable diminution in the optic neuritis. The patient, however, was satisfied that his vision was more acute than formerly.

There was no constitutional disturbance following the operation, the wound by the time he had left the hospital being practically healed. He was lively and very talkative (natural state), being quite different from his irritable and despondent condition of the days before he was operated on.

Report on the Nature of the Growth by Dr. Archibald. The tumor, as removed, consisted of three large fragments and several small ones. The largest of these measured roughly about 3 x 3 x 1½ cm., the second about half this size, and the third still smaller. The periphery of the tumor was of a very dark grayish color, not unlike cerebral cortex. It merged gradually into a whitish substance, very friable and shreddy, which formed the interior of the growth, and which proved to be degenerated, half-necrotic substance. The whole was dotted over with numerous small hemorrhages.

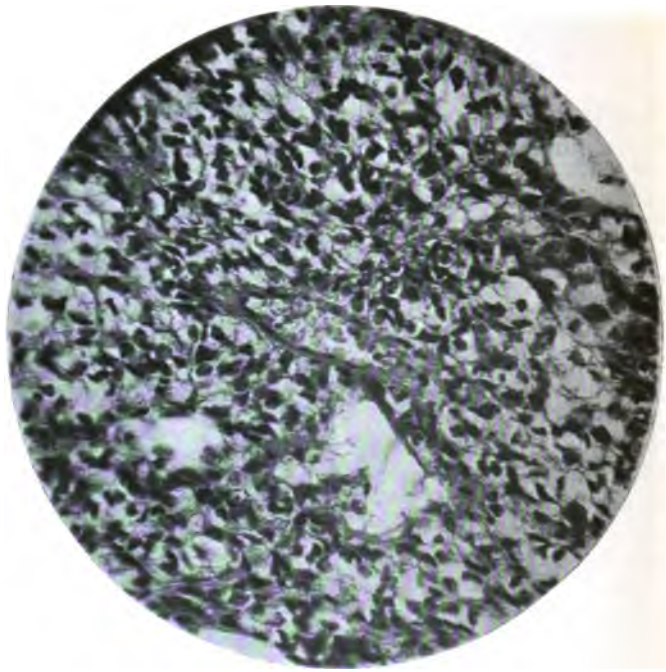
Macroscopically there was no distinct capsule; microscopically, however, one was found, consisting of a narrow rim of condensed fibrillary tissue, containing practically no cells.

Microscopic Examination. This is not yet complete; it is, however, sufficient to justify the diagnosis of glioma.

The outer, better preserved area shows a new growth, encapsuled as above mentioned, and consisting of cells fairly uniform in size, about twice that of an ordinary lymphocyte, but varying considerably in shape, some being round, others oval, pear-shaped, or even stellate. These cells lie in a very loose and fine stroma of fibrils, most of which do not apparently take Mallory's specific stain for differentiated glia fibers (modified fibrin methods). A few such, however, are found here and there; but whether they do not in this situation represent fibrin must remain as yet undecided.

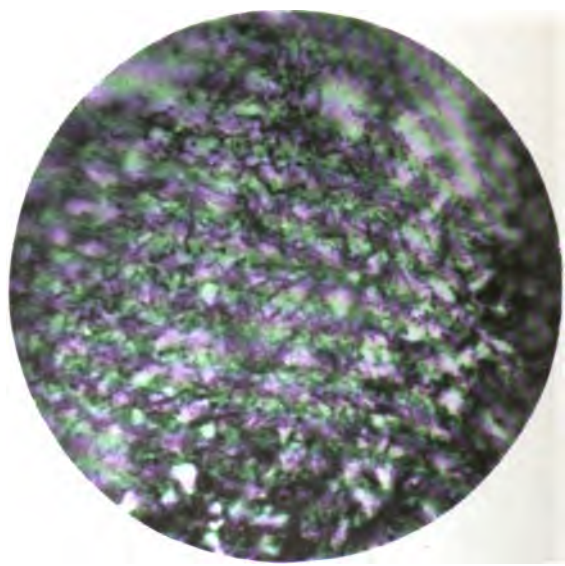
As one goes inward toward the older degenerated portion of the growth, these differentiated fibers, taking Mallory's stain, become more numerous and finally form a solid mass, in which comparatively few cells can be found. And these cells are, on the whole, smaller than the cells of the peripheral well-preserved area, and more uniformly round. They are, however, largely degenerated, and take any stain very poorly. The degeneration shows as a mass of granular detritus, and is probably albuminous in nature, as is said by Bonome (*Virchow's Archiv*, March 22d) to be frequently the case in gliomata.

FIG. 1.



Represents a portion of the periphery of the tumor, stained by hematoxylin-eosin, embedded in paraffin.

FIG. 2.



Represents a spot from the necrotic shreddy material of the center, showing practically nothing but a tangle of neuroglia fibers, stained deep violet by Mallory's neuroglia stain. His phosphotungstic acid hematoxylin has not so far given satisfactory results.

There is no trace of nerve tissue in the tumor. This was confirmed by Dr. Shirres, clinical assistant in neurology, who kindly examined sections with regard to this point.

New-formed vessels are found in abundance, together with frequent small local hemorrhages.

Around some of the old vessels there appears to have occurred a fibrous tissue proliferation, the spindle cells of which arrange themselves in a radiating way around the circumference. This is, however, infrequent; and the hypothesis of a sarcoma beginning in vessel adventitia may, so far as present sections allow one to judge, be excluded.

To resume: We have had a tumor of widely differing histologic characters. In the center a mass of differentiated glia fibers with very few cells; at the periphery a richly cellular growth, not unlike sarcoma at first sight, but merging by transition stages into the structure of the center. There seems, then, to be some ground for the conclusion that the whole is of the gliomatous nature, and that in a glioma there may be one portion, presumably of youngest, most recent growth, the cells of which have not yet the property of producing differentiated neuroglia fibers, while another portion consisting of older or oldest cells may, having acquired this property, show large numbers of such differentiated fibers, even to the almost total exclusion of cells. A consideration of this question will, it is hoped, throw some light on the vexed question of the so-called gliosarcomata.

There has not been sufficient time for the thorough working out of this growth, nor for a complete examination of the literature, and the above must be regarded as a preliminary note. It is hoped, however, in a later article to present a more detailed description and a more extended consideration of the subject as a whole. Two microphotographs are appended.

SUMMARY. The following summary of the course of the symptoms in this case will make it more clear and definite:

A man, aged thirty-seven years, without previous warnings, suddenly became speechless for about twenty minutes. There was a recurrence of attacks of a similar character every few days for a period of several weeks. Then severe headache and optic neuritis supervened, and afterward facial spasm followed by paresis of the lower facial muscles on the right side, as well as weakness of the right half of the tongue. The mutism no longer was noticed, its place being taken by a dysarthria, first of labials and later of all letters and words, and finally passing on to a practically complete anarthria.

On opening the brain a tumor was found immediately beneath the gray matter of the lower part of the ascending frontal convolution. The removal of this was easily accomplished, and was followed in the course of a few days by disappearance of the anarthria and the facio-

lingual paralysis. The patient is now, two months after the operation, practically well, there being no evidence, except slowness of speech, of any disturbance of the central nervous system.

The case is interesting on account of:

1. As being an instance of a successful removal of a subcortical growth, the location of which had been correctly made out six weeks previous to the operation.

2. As showing that dysarthria and not aphasia is the characteristic form of speech disturbance met with in growths in this situation. The growth was situated so as to compress the speech tract some distance from the motor speech center, but still sufficiently near to involve the commissural fibers that pass over to the right hemisphere in the corpus callosum. Following the lead of Lichtheim and Dejerine, it has been the custom with even the most recent writers to call the speech disturbance attending lesions in this situation subcortical motor aphasia.

Bastian in his recent able work on *Aphasia* clearly shows that these subcortical lesions do not give rise to aphasia, but to dysarthria or anarthria. This case bears out his view.

It would certainly be erroneous to call the speech disturbance aphasia. An aphasic patient is able to utter some word, and when he does do so the articulation is perfect, whereas in anarthria, when more or less complete, even the simplest words and individual letters are scarcely recognizable.

To distinguish between the anarthria of subcortical lesions and that produced by lesions of the bulbar nuclei, Bastian uses the term aphemia (speechlessness) for the former and anarthria for the latter. It must, however, be understood that there is no clinical difference between the speech disturbance of subcortical lesions and that brought about by bulbar lesions. They are recognized by the collateral symptoms. In nearly all cases reported of so-called subcortical motor aphasia it is claimed that defects in writing did not occur.

Here there was a marked disorder in writing—an ataxia of writing, or what might fairly be named a dysgraphia. This was present without any weakness of the right hand, and was, therefore, not due to loss of power, but rather to disturbance of co-ordination. Considering the near situation of the lesions to the centers of the hand, it is not surprising to find and not difficult to account for the disability in writing.

PSEUDOMEMBRANOUS INFLAMMATION OF THE MUCOUS MEMBRANES CAUSED BY THE PNEUMOCOCCUS.

Review of the Literature and Report of a Case of Pneumococcic Pseudomembranous Exudation on the Mucous Membranes of the Mouth, Tongue, Throat, Nose, Eyes, Glans Penis, Anus, etc., Complicating Acute Lobar Pneumonia.

By CHARLES CARY, M.D.,

AND

IRVING PHILLIPS LYON, M.D.,

OF BUFFALO, N. Y.

The case here reported is remarkable in one respect only, *i. e.*, the occurrence, during the course of an attack of acute lobar pneumonia in a boy of eleven years, of a profuse pseudomembranous exudation upon nearly all the mucous surfaces of the body open to inspection, caused by the pneumococcus (diplococcus pneumoniæ). In addition to the visible fibrinous exudate upon the mucous membranes exposed to view, the case also showed signs of extensive adhesive pleuritis and marked and continued tympanites, with the passage of membranous shreds in the stools, leading to the belief that the fibrinous process involved also the pleuræ and the gastro-intestinal tract. Aside from these features the case showed nothing remarkable, pursuing a severe and protracted course which terminated by gradual lysis, with recovery. The case will, therefore, be reported chiefly with referene to the unusual complications, omitting unimportant details relating to the more usual features of the disease —from the clinical side by Cary, who had charge of the case throughout, and from the pathologic side by Lyon, who saw the case for the first time on January 17th in consultation with Cary—as follows:

Summary of case: Acute lobar pneumonia of both bases, with development during the first ten days of a profuse pseudomembranous exudate, first upon the tonsils and quickly extending to the mucous membranes of the lips, tongue, mouth, palate, throat, and nose, and transferred to the eyes, glans penis, and anus; physical signs of fibrinous pleuritis; marked and persistent tympanites; membranous shreds and mucus in the stools. Microscopic examination: bacillus diphtheriæ, streptococcus, saccharomyces albicans, etc., absent; diplococcus pneumoniæ present in abundance in the sputum and in the exudate from all locations, grown in cultures and injected into a rabbit and recovered from the organs and blood after death. Diagnosis; pneumococcic infection resulting in acute pneumonia, pleurisy, and fibrinous exudation upon the mucous membranes. T. R., aged eleven years, a boy somewhat undersized and undeveloped for his age, of the best social condition and surroundings, was taken ill on January 5, 1901.

Family History. Negative.

Personal History. The patient has had the usual diseases of childhood. He had been a mouth-breather from enlarged tonsils, which were excised five years ago, since which he has been subject to frequent and severe attacks of follicular tonsillitis, of which as many as eight or nine sometimes occurred during a single season. Throat cultures made during these attacks always proved negative for the diphtheria bacillus. During the past year only a single attack of tonsillitis occurred. One year ago he had a short, slight attack of catarrhal pneumonia, from which he recovered without incident.

Present Illness. The present illness began on January 5, 1901, with sore-throat and fever, which were supposed by the boy's mother to indicate the onset of one of his accustomed attacks of tonsillitis, and he was treated with the usual remedies. On January 7th the family physician, Dr. Cary, was called, and found a reddened sore-throat (without exudation), signs indicating early involvement of the base of the left lung, and temperature 103.5° F., pulse 114, and respirations 42. Next day the temperature was 104° F., pulse 130, respirations 40, and the signs of pneumonia at the left base were more marked. On January 11th signs of consolidation of the right base also appeared, and the patient complained of a painful sore-throat. Examination showed an abundant white exudate covering both tonsils, from which a culture was made and was reported negative for the diphtheria bacillus by Dr. Thomas B. Carpenter, bacteriologist of the City Board of Health. In the meantime a marked vesicular eruption had appeared over the chest, following directly the application of turpentine and oil (1 : 6). The vesicles were numerous, discrete, and reached the size of a five-cent piece in some instances, and the sores left by them were an annoying feature in the early part of the illness.

On January 12th a herpetic eruption appeared upon the lips; the exudation was more or less general throughout the mouth and throat, and the eyes were the seat of a beginning conjunctivitis. Dr. H. Y. Grant, oculist, was placed in charge of the eyes, and active treatment was directed to them. On January 13th there was marked fibrinous conjunctivitis, and subconjunctival hemorrhages were scattered over the eyes, the lids were swollen and adherent,

and photophobia was complained of. The mucous membranes covering the lips, gums, cheeks, margin and under surface of the tongue, hard and soft palate, fauces, tonsils, pharynx (as far back as could be seen), and nose were covered with a continuous, white, adherent exudate, which could be torn off in shreds and pieces, sometimes as large as a twenty-five-cent piece, leaving behind a raw, granular, bleeding surface. The boy could not be restrained entirely from picking at his nose and lips, and his fingers were seen to be bloodstained. He thus apparently transplanted the infection from one place to another.

On the evening of January 15th the glans penis (circumcised) became involved in the same membranous process, and next day was covered in its greater part by a thick, raised, adherent membrane, which extended to the meatus and caused the lips to be glued together, producing difficulty in micturition by pressure. The process did not, however, extend into the urethra. The membrane could be torn off in pieces, leaving behind a raw bleeding base similar to that seen in the mouth after removal of the exudate.

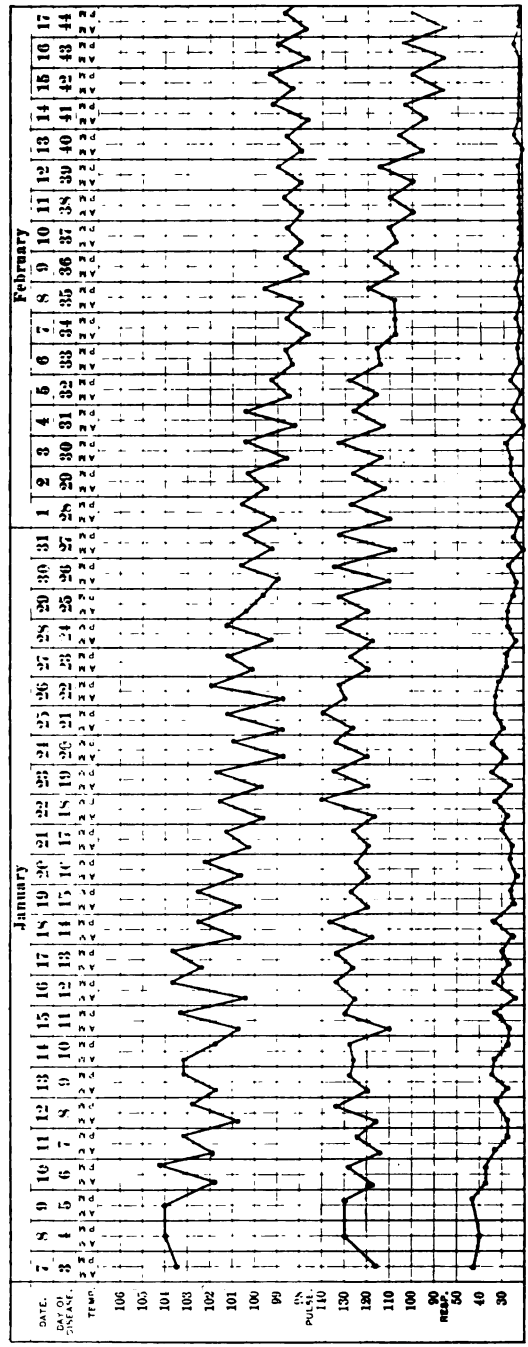
At this time a large piece of the membrane obtained from the mouth was submitted to Dr. Herbert D. Pease, bacteriologist to the New York State Pathologic Laboratory of the University of Buffalo, who reported negatively for the diphtheria bacillus, but noted the presence of frequent diplococci, the nature of which, however, was undetermined, as the examination was somewhat cursory.

Next day, January 16th, an examination showed the anus also involved in a membranous deposit, and the nurse first noted the presence of membranous shreds in the stools. The deposit on the anus extended within the sphincter, though to what distance was not determined, as a speculum could not be introduced without much pain. A shred about two inches long was removed through the anus by winding it upon a match. For several days the abdomen had been distended, with marked tympanites. The stools had been rather frequent, soft, contained considerable mucus, and much gas was expelled. The spleen was not palpable, and no rose spots appeared.

At this time the disease was at its height. Both lower lobes were consolidated. The membranous exudate was profuse and showed no signs of yielding to active local treatment. The breathing was noisy and labored, with seeming suffocation from the accumulation of mucus in the upper air passages. The expectoration, which was mostly swallowed, was thick, viscid, mucopurulent. The cough was constant, deep, and gagging. About this time, also, signs of extensive fibrinous pleuritis became marked, chiefly over the left base; the right base was also involved, but not so frankly. The pleural friction over the left base could be felt with the hand on the chest, as well as heard with the stethoscope. The patient's condition seemed critical.

On January 17th the case was first seen by Dr. Lyon in consultation with Dr. Cary, when the disease was at its height, and the following examinations were made by him:

Blood. Leukocytes, 16,600; hemoglobin, 70 per cent. Differential leuko-


DATE.
DAY OF DISEASE.
TEMP.
PULSE.
RESP.
January
February

cytic count: neutrophiles, 81 per cent.; small lymphocytes, 12 per cent.; large lymphocytes, 6.5 per cent.; eosinophiles, 0.5 per cent.; 400 counted. Red corpuscles well formed; an occasional normoblast. Fibrin increased. Widal test negative.

Sputa. Mucopurulent, yellowish-white in color, with an occasional reddish streak. Microscopically it showed numerous pus cells, epithelial cells, sometimes containing brown granules (blood detritus), mucus, and fibrin; occasional red blood-corpuscles; a few very small fibrinous casts of the finer tubules with dendritic processes attachd. Stained specimens showed numerous large diplococci, with wide capsules, morphologically identical with the diplococcus pneumoniæ. This organism stained by Gram, but the capsule was not clearly stained by Welch's method.

Membranous Exudate from Lips. Thick, white, gelatinous material, which was partly soluble in water, which latter gave the chemical reactions for mucin. The undissolved residue showed typical fibrin filaments, and stained by Weigert's method. Stained specimens showed in abundance the same diplococci as found in the sputa, as well as an occasional single coccus. Numerous epithelial cells and leukocytes and much detritus were also found in the exudate. The *diphtheria bacillus, streptococcus, saccharomyces albicans, etc., absent.*

Membranous Exudate from Nose, Glans Penis, and Anus. All of these specimens were similar grossly and microscopically to the pseudomembrane from the mouth, all containing the same encapsulated diplococcus in large numbers, practically in pure culture, except the membrane from the anus, which showed, in addition to the diplococcus, contamination with the usual fecal flora. [It is worthy of note that in the case of the glans penis the exudate was not deposited upon a true mucous membrane, as was the case in all the other locations, for the boy had been circumcised in early childhood.]

Exudate from Conjunctivæ. This was flaky, and did not take the form of a uniform membranous deposit, as in the other locations involved. The same organism was found (pure) as in the other specimens, though less numerously, probably due to the active and continued treatment which the eyes had received (frequent irrigation, etc.).

Fæces. Nothing characteristic was found except the same diplococci found elsewhere. The single specimen examined contained much mucus, but no fibrinous shreds.

Cultures. Pure cultures of the pneumococcus were obtained from the exudate from the eyes and nose, and mixed cultures of the pneumococcus and the staphylococcus pyogenes aureus from the membrane from the mouth and from the sputa. The diplococcus did not grow upon potato, and did not liquefy gelatin. It grew upon blood-serum, agar, glycerin-agar, and bouillon. It coagulated litmus milk, with the production of an acid reaction.

Inoculation. One minim of a suspension of the nasal exudate in normal saline solution was injected into the peritoneal cavity of a rabbit, which died in twenty-two hours with general peritonitis and septicemia. The pneumococcus was obtained in pure culture from the heart's blood, organs, and

peritoneal exudate. Stained smears from the heart's blood showed the pneumococcus typically in pairs, occasionally in short chains, with a wide capsule surrounding.

Urine. Several urinalyses were made by Dr. G. A. Himmelsbach, showing a trace of albumin, without casts, and the general characteristics of an acute febrile urine.

The eyes were practically clear and free from the exudate by January 28th. The mouth, throat, nose, and anus at this time showed improvement, but the exudate was still present in these locations in considerable amount. The membrane on the glans penis was less resistant and tended to dry up and disappear after a few days with active treatment. Gradually, after another week or ten days, the deposit over the other locations disappeared, after persisting for about four weeks in spite of active local treatment with various antiseptics. The tympanites lasted about two weeks and was a prominent feature of the disease. The termination of the pneumonic process was by gradual lysis, as shown by the accompanying chart. The boy was allowed to sit up for the first time about the middle of February, and convalesced slowly. Slight dulness with pleural crepitation persisted over the left base, and was present when the boy was last examined, April 20, 1901.

Little remains to be said of this case after the recitation of the facts. That the production of a pseudomembranous exudate upon the various mucous membranes was caused by a specific local action of the pneumococcus cannot be doubted in view of the bacteriologic findings. That the pneumococcus is capable of causing such lesions is attested by the reports of various observers. This case appears to be unique, however, in the wide extent of the process. Not only were involved nearly all the mucous membranes of the body that could be inspected, but probably the gastrointestinal tract as well, as evidenced by the prolonged tympanites and the passage of membranous shreds and mucus in the stools. No other reported case has shown such a wide distribution. It is noteworthy also that the process was not entirely confined to the true mucous membranes, as the glans penis had been circumcised in early childhood. The infection seemed to have been transplanted from one place to another by the boy's fingers, which were bloodstained from picking at his nose and lips. The pleuræ of both sides were apparently involved in an extensive fibrinous pleuritis, and small fibrinous casts of the finer tubules were found in the sputa. All of these phenomena occurred as complications in the course of acute lobar pneumonia. There were fortunately no signs of endocarditis or pericarditis.

As but few cases of pneumococcic pseudomembranous inflamma-

tion of the mucous membranes are recorded in the literature, and most of these are of recent date, it will probably add to the interest and instruction of our case to briefly review the cases that we have been abe to collect from the literature by a rather diligent search. Most of the text-books of medicine make no reference to such a process. The cases may be divided as those occurring in association with pneumonia and those occurring as a purely local infection independent of a pneumonic process, as follows:

Cases of Pseudomembranous Inflammation of Mucous Membranes Occurring in Association with Pneumonia. This class includes (*a*) cases in which the pneumococcic origin of the croupous exudate upon the mucous membranes was not proved, but merely suggested by its association with pneumonia, and (*b*) cases in which the pneumococcus was shown by bacteriologic methods to be the specific agent in producing the lesion.

(*a*) *Pneumococcus not Found.* The earliest reference to croupous inflammation of mucous membranes as a complication of pneumonia that we have found is the statement by Bristowe,[1] in 1879, that "sometimes membranous patches on the mucous surface of the large intestine" occurred in acute pneumonia.

Osler[2] was the next (1885) to point out the same condition, reporting five cases of "croupous colitis" in one hundred autopsies on subjects dead of pneumonia. The process was represented usually by a "thin, flaky exudation involving only the surface of the mucous membrane. In none of the cases was there ulceration." "In one case (Case III.) the cecum was covered with a thin layer of adherent lymph, and scattered throughout the colon and sigmoid flexure there were numerous elevated patches of lymph, about the size and shape of rupia-crusts, which on section were found firmly attached to the mucosa. In this instance the process was very extensive, and the patches were thicker than in any subsequent case." In another case in this series of one hundred autopsies (Case IV.) "the stomach and duodenum were found greatly distended with gas. The mucosa was pale, except about the fundus, where, just to the left of the cardia, there was an extensive area of croupous inflammation, represented by a thick, adherent, grayish-white exudate, covering an area 12 by 8 cm. Beneath the mucosa the membrane was deeply injected."

Massalongo[3] is also credited with having reported a case of pseudomembranous enteritis as a complication of pneumonia.

Bardon[4] reported the case of a man, aged twenty-four years, who developed in the stage of resolution of pneumonia a pseudomembranous angina involving the entire pharynx.

(*b*) *Pneumococcus Found.* Weichselbaum[5] mentions briefly a case of lobar pneumonia and pleurisy with croupous enteritis. The pneumococcus was found in the intestinal croupous exudate, and was demonstrated by inoculation in animals.

Netter[6] observed a boy, aged three years, with varicella and urgent symptoms of laryngitis requiring tracheotomy, through the wound of which a false membrane was expelled, containing no diphtheria bacilli, but "only pneumococci with beautiful capsules and of average virulence." After some days bronchopneumonia of both bases supervened; recovery.

Rochon[7] described the following interesting case: A boy, aged two years, in the course of an attack of whooping-cough, developed severe and continued diarrhea, with an eruption of vesicles about the anus. The examination of the clear contents of the vesicles, obtained with aseptic precautions, showed "pneumococci in pure culture" in smear preparations. During a severe fit of coughing on the eighth day of the diarrhea a prolapsus of the rectum occurred, revealing the mucous membrane covered in places with a pseudomembranous exudate, which was removed with difficulty, leaving a red, granular base. The exudate, stained by Gram, showed "numerous pneumococci." Pneumonia of the upper portion of the left lung developed on the tenth day of the diarrheal process, and death followed on the next day.

A. and V. Vedel[8] described the case of a child, aged two years, with bronchopneumonia at the left base and extensive pseudomembranous deposit involving the entire pharynx and the palate, lips, and nasal cavities; death after seven days, from heart failure. In the pseudomembrane the pneumococcus was found in a state of purity, grown in pure culture, and proved fatal to a white rat after injection.

Ballay and Halipre[9] reported the case of a child, aged thirteen months, with bronchopneumonia, croupous exudate on both tonsils, and symptoms of laryngeal stenosis, supposed to be croupous, re-

quiring intubation. Cultures from the tonsillar pseudomembrane showed only the pneumococcus. On the twelfth day purulent otitis media developed, but no bacteriologic examination of the discharge from the ear was made. Convalescence was established on the twenty-fourth day.

Comby[10] stated that he had seen pneumococcic angina in two cases in infants precede pneumonia, which at first had the appearance of diphtheria.

Griffon[11] observed in a butcher, twenty-nine years old, in the course of acute pneumonia, a pseudomembranous inflammation involving the buccal mucous membrane opposite the molars on the left side, both tonsils, the palate, and the pharynx in an extensive network. Pure cultures of the pneumococcus were obtained from the pseudomembrane, and proved fatal to a mouse after injection. The croupous exudate disappeared in a few days. Tympanites was noted. A specific agglutinating reaction was claimed to have been obtained on cultures of the pneumococcus with the patient's blood.

Cases of Pseudomembranous Inflammation of Mucous Membranes of Pneumococcic Origin, Independent of Pneumonia. Jaccoud,[12] who claims priority (1891) in establishing the existence of pseudomembranous angina caused by the pneumococcus, reported the case of a young man, nineteen years of age, who was suddenly taken with a chill and fever, and showed on the second day a pseudomembranous exudation on both tonsils, the anterior pillars of the fauces, and the uvula. The false membrane showed all the histologic characteristics of the true diphtheritic membrane, except the presence of the Klebs-Loeffler bacillus. Ménétrier, who made the bacteriologic examinations, found "pneumococci in great abundance and almost pure" in the exudate, and cultures and inoculation experiments made by him "leave no doubt in this regard," *i. e.*, the pneumococcic origin of the process. The pseudomembranous process had ceased its activity by the ninth day, and the patient was well on the seventeenth day of the disease.

The same author[13] reported two similar cases in 1893, one a woman, aged twenty-six years, the other a girl of seventeen years, both with pseudomembranous inflammation of the tonsils, which made its appearance on the second day of the illness. In both cases Martin found "pneumococci in abundance in a state of

purity, or sometimes accompanied by streptococci." The onset of the disease was marked by chill, shaking, and abrupt rise of temperature. Both cases terminated with recovery in three or four days. Based upon his three cases, Jaccoud attempted to draw a differential picture of pneumococcic angina, characterized by sudden onset, with chill, shaking, abrupt rise of temperature, short duration, and favorable course.

Seuvre[14] observed a boy, eight years old, who, in the course of an attack of grippe, developed an erythematous angina with signs of laryngeal stenosis, requiring tracheotomy, through the wound of which a false membrane was expelled giving a pure culture of pneumococcus. Diphtheria bacilli were absent.

Comba[15] reported a case of pseudomembranous tonsillitis and double pseudomembranous conjunctivitis in a child of seven months, due to the pneumococcus.

Abel[16] reported a pseudomembranous inflammation in a boy of thirteen years, limited to the anterior nares, which finally disappeared after fourteen days. The deposit showed pneumococci in great abundance and a very few other organisms, but no diphtheria bacilli. Cultures and animal experiments showed that the pneumococcus was the only pathogenic organism in the exudate.

The earliest reference to pseudomembranous conjunctivitis ascribed to the pneumococcus is in the thesis by Morax,[17] who reported four cases from Parinaud's clinic, observed in the autumn of 1893, in infants ranging from eight days to two and one-half years in age. The process was characterized by the presence of pseudomembranous exudation on the lower lids, in which the pneumococcus was found pure and in abundance. The organism was grown in pure culture and recovered from animals dead after injection. The affection was always unilateral, running a short and benign course. The bulbar conjunctiva was never involved in the deposit.

Parinaud[18] reported cases of lacrimal conjunctivitis in the newborn in the first few days of life, showing fibrinous deposits or flakes mixed with the tears in the inferior cul-de-sac. In twelve cases the pneumococcus was found in abundance in the conjunctival secretion and grown in pure culture by Morax. The gonococcus and Weeks bacillus were totally absent. "This pneumococcic con-

junctivitis of the newborn, as well as that of older infants, which Morax and I have described, may become pseudomembranous without ceasing to be benign, at least according to my observation."

Gifford[19] reported cases of pure pneumococcus conjunctivitis, and stated that he had also observed in these cases, as previously pointed out by Gasparini,[20] a fine pellicle of fibrin which could be wiped off from the everted upper tarsus, which had not been observed in conjunctivitis due to the Weeks bacillus.

Axenfeld[21] encountered a school epidemic of conjunctivitis, involving twenty-four persons, showing pseudomembranous flakes. Cover-glass specimens, as well as cultures from the pseudomembranous exudate, showed characteristic pneumococci, and they were confirmed as such by Professor Behring. Animal inoculations resulted in typical pneumococcus septicemia. The process ran its course in from three to ten days. Small ocular subconjunctival hemorrhages were noted.

As will have been observed, most of these reported cases of pneumococcus conjunctivitis were of a character that could hardly be described, strictly speaking, as pseudomembranous—*i. e.*, with an adherent fibrinous exudate on the conjunctiva—but were characterized by the presence of small fibrinous shreds in the exudate of the eye, sometimes lightly adherent to the mucous membrane of the lids. As a similar condition may often be found in the eye in almost any kind of acute conjunctivitis, it seems impracticable to draw any sharp and fast distinction between such cases and those that are more positively of a pseudomembranous nature. Within the past five years rather numerous cases[22] of pneumococcus conjunctivitis have been reported, but they have generally been without any definite pseudomembranous deposit. Such was the condition, also, in the case which we have described. The explanation of the relative freedom of the eye from croupous deposits is doubtless found in the mechanical difficulties offered to the development of such a process by the natural irrigation and drainage of the eye.

In addition to the above cited cases, which were reported more or less circumstantially, occasional references are also found in the literature to possible cases of true pneumococcic pseudomembranous angina, in which the pneumococcus is merely mentioned as occasionally found in or grown from the croupous exudate in a small percent-

age of a long series of cases of croupous angina studied bacteriologically, as, for instance, in the reports by Carl Janson,[23] De Blasi and Russo-Travali,[24] Cassedebat,[25] and others. The mere mention of finding pneumococci in such cases cannot, of course, be accepted as proof of the etiologic relation of this organism to the morbid process, for it is well known that occasional pneumococci may be found in the throats of a considerable proportion of healthy persons, usually estimated at 20 per cent., and can be grown in culture from such throats. Therefore, unless the pneumococcus be found in pure culture, or else as the predominating organisms in the exudate, its presence is of not much significance.

The above cases, in which the pneumococcus was demonstrated as the cause of a local croupous inflammation, have all been reported within the last dozen years, and it is thus shown how recent is the recognition of the pneumococcus as an agent capable of exciting localized pseudomembranous inflammation of the mucous membranes of different parts of the body. Doubtless it is not so rare an agent in this condition as might be supposed from the paucity of reported cases, and will be shown by future investigation to be a not uncommon cause of pseudomembranous inflammation of the mucous membrane outside of the lungs.

There is nothing to distinguish the nature of the process from the similar condition associated with the diphtheria bacillus or the streptococcus, except the bacteriologic examination, which should be made in all cases of pseudomembranous inflammation. The clinical course described by Jaccoud,[26] Weinberg,[27] and Gaultier[28] as characteristic of pneumococcus croupous angina* had no counterpart in our case, and would be of no value for excluding diphtheria,

* We have limited ourselves in this paper to a discussion of pneumococcic inflammation resulting in pseudomembranous exudation. It might be remarked, however, that the pneumococcus has been demonstrated as the cause of inflammation of the mucous membranes of all the following varieties: erythematous, follicular, herpetic, pseudomembranous, and suppurative. For a comprehensive discussion of these different varieties of pneumococcic angina and cases from the literature up to 1896, see Gaultier's thesis (loc. cit.). In view of the occurrence of a herpetic or vesicular form of inflammation and the discovery of the pneumococcus pure in the contents of the vesicles, both in the throat and about the anus, it would be interesting to make observations on the contents of the herpes labialis, so commonly seen in pneumonia. It appears likely that these vesicles are caused by a local development of pneumococci, which would be found in the contents of the vesicles. We regret that such examination was not made in our case, and that we did not also examine the contents of the large vesicles that developed upon the chest, though in the latter case we, naturally enough, assumed the eruption to be merely the result of the local irritation of the turpentine that had been applied.

which may show the same clinical picture. As a rule, the cases have been mild, and after a short course have ended in recovery. How refractory to treatment, how long continued, and how infectious the process may exceptionally be are illustrated by our case. Most cases occur in childhood, though adults in the prime of life are sometimes affected. The mucous membranes of almost any part of the body may be involved, as illustrated by the cases cited. The process may be very limited or very extensive and almost general. It may occur in association with pneumonia during some part of its course, or may be quite independent of any pulmonary involvement. Local germicidal agents have usually been employed with apparent success, but failed entirely to have any good effect in our case. Whether due to it, or independently of it, and merely coincident with its use—we would not venture an opinion—the process tended rather promptly to ameliorate and disappear upon the administration by mouth of drachm doses of fresh brewer's yeast.

In conclusion, we take pleasure in acknowledging our indebtedness to Professor William H. Welch, of Baltimore, for his very generous assistance in referring us to cases in the literature.

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OBSERVATIONS ON THE FREQUENCY AND DIAGNOSIS OF THE FLINT MURMUR IN AORTIC INSUFFICIENCY.

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In 1862, Austin Flint, in an article on cardiac murmurs,[1] called attention to the occasional existence, in uncomplicated aortic insufficiency, of a presystolic murmur limited to the region of the cardiac apex, and distinct from the characteristic murmur of aortic regurgitation. This sound occurred in the latter part of diastole, was loud and blubbering, and had all the characteristics of a mitral direct presystolic murmur. Flint recognized it as such, and offered the following explanation: "The explanation involves a point connected with the physiologic action of the auricular valves. Experiments show that when the ventricles are filled with a liquid the valvular curtains are floated away from the ventricular sides, approximating to each other and tending to closure of the auricular orifice. In fact, as shown by Drs. Baumgarten and Hamerik, of Germany, a forcible injection of liquid into the left ventricle through the auricular opening will cause a complete closure of this opening by the coaptation of the mitral curtains, so that these authors contend that the natural closure of the auricular orifices is effected not by the contraction of the ventricles, but by the forcible current of blood propelled into the ventricles by the auricles. However this may be, that the mitral curtains are floated out and brought into apposition with each other by simply distending the ventricular cavity with liquid, is a fact sufficiently established and easily verified. Now, in cases of considerable aortic insufficiency the left ventricle is rapidly filled with blood flowing back from the aorta, as well as from the auricle before the auricular contraction takes

[1] American Journal of the Medical Sciences, 1862, iv. s., xliv. 29.

place. The distention of the ventricle is such that the mitral curtains are brought into coaptation, and when the auricular contraction takes place the mitral direct current passing between the curtains throws them into vibration and gives rise to the characteristic blubbering murmur. The physical condition is, in effect, analogous to contraction of the mitral orifice from an adhesion of the curtains at their sides, the latter condition, as clinical observation abundantly proves, giving rise to a mitral direct murmur of similar character."

In 1883, Dr. Keyt,[1] while disputing Flint's explanation of the origin of the murmur, suggesting that it might arise at the aorta in systole, proposed that it be called the murmur of Flint, a term which has since been used by many. In 1883, Flint[2] recorded another observation of the same nature, and in 1886 discussed the subject at length in an article in *The American Journal of the Medical Sciences*.[3] Since this time the phenomenon has been recognized by numerous clinicians.

Most observers who have recognized the Flint murmur have agreed on considering its occurrence unusual. Guitéras, however, sixteen years ago,[4] expressed the belief "that obstructive functional mitral murmurs are of frequent occurrence in aortic regurgitation." He suggested that the obstruction offered by the partially closed mitral valves, at the time of the entrance of the auricular blood, might serve in the manner of a safety-valve and help to prevent over-distention of the ventricle. Guitéras[5] reported three characteristic cases and expressed a modification of Flint's theory as to the manner of origin of this murmur, asserting that in aortic regurgitation the mitral leaflets are not "floated upward," but are actively driven against the auricular blood by the force of the general arterial tension; that such force is, in all probability, often exerted against the anterior leaflet of the mitral valve by a regurgitant current which falls directly upon it.

Osler[6] also asserts that this murmur occurs in a considerable proportion of all cases.

[1] Boston Medical and Surgical Journal, 1883, cix. 30.
[2] Lancet, London, 1883, i. 131.
[3] American Journal of the Medical Sciences, 1886, xci. 35.
[4] Medical News, Philadelphia, 1885, xlvii. 533.
[5] Transactions of the Association of American Physicians, 1887, ii. 39; also, Boston Medical and Surgical Journal, 1887, cxvii.
[6] Practice of Medicine, New York, 1898, 8vo., 3d ed., p. 714.

In Gibson's recent work,[1] after a thorough discussion of Flint's description of this murmur, and a review of the literature on the subject, there appear the following words: "Being thoroughly conversant with Flint's views since the appearance of his second paper, the points under discussion have been diligently sought for by us; so far, however, without result. Cases have frequently presented themselves, no doubt, in which, with absolute evidence of aortic disease, there has been a presystolic murmur, but in every one of these, without exception, post-mortem examination has revealed mitral obstruction as well as aortic lesions."

My attention was first called to the subject fourteen years ago by Guitéras' article, and two years later, while house physician at the Massachusetts General Hospital, I had the good fortune to observe a case in which my diagnosis of Flint murmur was confirmed by necropsy. Since that time I have been impressed with the fact that the Flint murmur is a far commoner manifestation than might be inferred from the usual statements in literature. It has, therefore, seemed to me that it might be of considerable interest to analyze the clinical and pathologic records of those cases of aortic insufficiency which have come to necropsy in Professor Osler's clinic at the Johns Hopkins Hospital.

A majority of these cases have been under my personal observation.

The purpose of this investigation is to reach some conclusion as to the frequency of this phenomenon and the grounds upon which a diagnosis may be made *intra vitam.*

Inquiry into the exact physical cause of the murmur will be beyond the limits of this communication.

Since May, 1889, 74 cases of aortic insufficiency have come to necropsy at the Johns Hopkins Hospital. In 45, or 60.8 per cent., of these cases there was heard, at some time during the observation of the patient, a rumbling, echoing murmur in diastole, limited to the region of the apex, and differing from the diastolic murmur of aortic insufficiency; in other words, a murmur exactly similar to that characteristic of stenosis of the mitral valve. This murmur, in the great majority of instances, was truly presystolic in time, ending

[1] Diseases of the Heart and Aorta, Edinburgh, 1898, 8vo. p. 497.

sharply in the first sound, or in a systolic murmur. In some cases it was separated by a short interval from the first sound, occurring in the middle of diastole.

In 12, or 26.6 per cent., of these cases there existed a stenosis of the mitral valve as well as aortic insufficiency.

In 33, or 73.3 per cent., the mitral orifice was of normal or increased circumference.

In all of the 12 cases in which there was an actual mitral stenosis, the anatomic lesion was an endocarditis. In one instance there was also general arterio-sclerosis.

Of the remaining 33 cases without mitral stenosis, the endocardial changes were part of a general arterio-sclerotic process in 16; in 17 there was chronic or acute endocarditis. In 4 of these latter instances there was a general arterio-sclerosis as well.

Of the 33 cases of aortic insufficiency in which, without mitral stenosis, a rumbling, vibratory presystolic murmur limited to the region of the apex was observed, the condition of the mitral valve, beyond the dilatation of the orifice which is the rule in well-marked aortic insufficiency, was absolutely normal in 17 instances.

In 16 greater or less change was present.

Of these 16 cases, in 4 instances the changes consisted simply in a slight thickening of the free edges of the curtains; in 8 the changes were those of chronic endocarditis without stenosis; in 3 there was subacute vegetative endocarditis, quite insufficient to have caused the presystolic murmur; in 1 there were rather large fresh vegetations, which might have been sufficient to cause a murmur in diastole.

Of the 16 cases in which there were changes in the mitral valve other than stenotic, the lesions were part of a general arterio-sclerotic process in 4, or 25 per cent.; in 12, or 75 per cent., the changes were those of chronic or acute endocarditis. In one of these cases there was also a general arterio-sclerosis.

Of the 17 instances in which the mitral orifice was normal, in 12, or 70.5 per cent., the changes in the aortic valve were secondary to a general arterio-sclerosis and atheroma of the aorta; in 5 there was chronic valvular endocarditis; in 3 of these latter cases there was also a general arterio-sclerosis.

In 29, or 39.1 per cent., of the 74 cases of aortic insufficiency no

presystolic murmur was heard. In 4 of these cases there was mitral stenosis.

Of the remaining 25 cases, in 10, or 40 per cent., the mitral valves were essentially normal; in the other 15, or 60 per cent., more or less marked chronic or acute alterations in the valves or chordæ tendinæ were present.

In 16, or 64 per cent., of these cases the process was apparently secondary to a general arterio-sclerosis; in 8, or 32 per cent., the condition was the result of chronic or acute endocarditis; in 1 the lesion of the aortic valves was apparently congenital.

On considering these figures one or two interesting facts become evident:

With Regard to the Frequency of Mitral Presystolic Murmur in Aortic Insufficiency Uncomplicated with Mitral Stenosis.

Out of 58 cases such a murmur was heard in 33, or 56.8 per cent.

One might insist that this percentage is too large in that I have included among these 33 instances 16 in which chronic or acute changes other than stenotic were present in the mitral valve. Might not these changes, after all, have played a certain part in the production of the presystolic murmur? While it may be, as held by Phear,[1] that marked shortening of the chordæ tendinæ alone may sometimes result in a presystolic murmur, yet this event is assuredly rare. And the following figures suggest that changes in the mitral valve other than stenotic have little effect on the production of a presystolic murmur:

Out of 27 cases of aortic insufficiency in which the mitral valve was anatomically absolutely normal, a presystolic murmur was heard in 17, or 62.8 per cent.

Out of 31 instances of aortic insufficiency in which the mitral valve showed greater or less change other than stenosis, a presystolic murmur was heard in 16 instances, or 51.6 per cent.

It would then appear to be clear that disease of the mitral valve other than stenosis has, in our cases, played no essential part in the production of a presystolic murmur.

[1] Lancet, 1895, vol. ii. p. 716.

The majority of our cases, then, of aortic insufficiency have showed, on careful examination, a Flint murmur—that is, a presystolic or late diastolic rumbling or echoing murmur heard in the region of the apex—a murmur clearly independent of organic mitral stenosis.

Is it Possible to Distinguish, Intra Vitam, Cases of Aortic Insufficiency with Flint Murmur from those Complicated with Mitral Stenosis?

It may be well to consider, first, the relative frequency of some of the more characteristic physical signs of mitral stenosis. The following are, perhaps, among the more important:

1. *The character of the pulse*, which, as a rule, is small, and, in condition of good compensation, of tolerably good tension, often irregular.

2. *The Character of the Cardiac Impulse.* The sharp, tapping, systolic shock is, perhaps, one of the most constant and characteristic signs of mitral stenosis.

3. *The thrill*, presystolic or sometimes mid-diastolic in time, and limited closely to the apex region.

4. *The evidences of right-sided hypertrophy* and the *accentuated second pulmonary sound*, which, however, are not especially important in the present consideration.

5. *The Presystolic Murmur.* There are few more characteristic signs than the rumbling, rasping or softer echoing, vibratory, crescendo, presystolic murmur, ending sharply, as it usually does, in a snapping first sound. Sometimes, when the heart's action is slow, there may be a momentary separation between the end of the rumbling murmur and the occurrence of the first sound.

6. *The Snapping First Sound.* The modification of the first sound is also a very characteristic element in mitral stenosis—the first sound which has the short, snapping, valvular character of a second sound. An element of this snapping sound is often present, even when a well-marked systolic murmur occurs.

In many instances when thrill and presystolic murmur are entirely absent a snapping valvular first sound, in connection with a small pulse, a dilated right heart, and an accentuated second pulmonic sound, may be sufficient to justify a diagnosis.

An analysis of the physical signs in 22 cases of uncomplicated mitral stenosis which have come to necropsy at the Johns Hopkins Hospital reveals the following facts:

1. *Pulse.* In all but three of these cases (86.3 per cent.) the pulse was of small size. In three instances where the stenosis was of very slight extent the pulse was described as of fairly good size.

2. *Thrill.* A thrill was present in 12, or 54.5 per cent., of the cases.

3. *Systolic Shock.* A tapping systolic shock was present in 15, or 68.1 per cent., of the cases.

4. *Snapping First Sound.* A characteristic snapping, valvular first sound was audible in 15, or 68.1 per cent.

5. *Presystolic Murmur.* A presystolic murmur, the most characteristic of the cardiac signs, was present in 17, or 77.2 per cent., of the cases.

The most important signs, then, of mitral stenosis in order of frequency are the presystolic murmur, the tapping shock of the first sound, the short, valvular, snapping first sound, the presystolic thrill, in association with the small pulse, the accentuated second pulmonic sound, and the enlargement of the right side of the heart.

Are these signs modified in cases of mitral stenosis combined with aortic regurgitation?

Let us examine our records with regard to the character of the signs in cases of this nature.

Sixteen such cases came to necropsy.

In 2 of these 16 cases there were no symptoms whatever of mitral stenosis. One of these was a case of marked aortic stenosis, with insufficiency and slight narrowing of the mitral orifice; in another case, seen only *in extremis*, but a slight presystolic thrill at the apex was noted.

1. *Pulse.* In 1 of these 16 instances, that combined with aortic stenosis, there was, naturally, a small pulse; in 4 the pulse was large and collapsing, but in 1 the statement is made that it was not of a typical Corrigan quality; in 3 it was noted that the pulse was of moderate size and collapsing; in 1 a collapsing character alone was mentioned; in 3 it was noted that the pulse was small, but collapsing; in 3 the pulse was small, but no especial mention of its aortic character was noted; in 1 it was especially noted that the pulse was not of aortic quality.

2. *Thrill.* Of these 16 cases, a presystolic thrill was present in 8, or 50 per cent.

3. *Systolic Shock.* A tapping systolic shock was noted in 7, or 43.7 per cent.

4. *Snapping First Sound.* A snapping first sound was heard in 12, or 75 per cent.

5. *Presystolic Murmur.* A presystolic murmur was present in 12, or 75 per cent.

The most constant and characteristic symptoms here, as in uncomplicated mitral stenosis, are the presystolic murmur and the tapping character of the first sound.

In 10 of these cases, where the aortic lesion was the more important, the degree of hypertrophy of the left ventricle was marked. In five, however, where the mitral stenosis was of considerable extent, there was but a moderate enlargement of the left side in association with a rather small pulse. In 1, where the aortic lesion was apparently primary, there was marked hypertrophy, with a small collapsing pulse.

The following table may serve to emphasize the modifications of the more essential signs of mitral stenosis observed in cases complicated with aortic insufficiency:

TABLE I.

	Uncomplicated mitral stenosis.	Mitral stenosis and aortic insufficiency.
Small pulse	86.3 per cent.	37.5 per cent.
Thrill	54.5 "	50 "
Tapping systolic shock	68.1 "	43.7 "
Snapping first sound	68.1 "	75 "
Presystolic murmur	77.2 "	75 "

A consideration of these figures would appear to show that the ordinary signs of mitral stenosis are not essentially changed when this condition is complicated with aortic insufficiency, with the exception of the fact that the pulse in the latter condition is often of a larger size and collapsing and—a modification of some interest—that the tapping character of the systolic shock is considerably less frequent.

Let us now compare with these figures the results of our analysis of the symptoms in 33 cases of aortic insufficiency with Flint murmur.

1. *The Pulse.* Of 33 cases of aortic insufficiency uncomplicated with mitral stenosis in which Flint murmur was heard, 1 was associated with aneurism of the aorta; 1 with a slight aortic stenosis, while in another the patient was moribund and the pulse was impalpable at the wrist. In 1 no satisfactory note could be found, and in another instance the only note was made toward the fatal termination of the case, during a pericarditis.

In the remaining 28 cases a typical Corrigan pulse was noted in 14, or 50 per cent. In 4 the pulse was of typically aortic character, with the exception of the fact that the size was hardly as large as is commonly noted. In 4 the pulse was collapsing, but no note was made of the size. In 1 the statement is made that the pulse is slightly collapsing in character. In 3 the pulse was said to be of a somewhat aortic character. In 2 it was simply noted that the pulse was compressible. In 1 the statement is made that the pulse was of fair volume and good tension.

In none of these instances was the pulse described as small.

2. *Thrill.* In 33 cases of aortic insufficiency with Flint murmur a palpable thrill was observed in 14, or 42.4 per cent.

3. *Tapping Systolic Shock.* A characteristic tapping systolic shock was noted in but 5, or 15.1 per cent., of the cases, and in 2 of these instances the tapping character was slight or inconstant.

4. *Snapping First Sound.* Of 33 cases of aortic insufficiency with Flint murmur the first sound was of a snapping valvular character in but 10, or 30.3 per cent. In 2 of these instances the snapping character was very slight, and in a third inconstant, having been noted only during attacks of tachycardia.

A better estimate of the differences in the physical signs in aortic insufficiency complicated with true stenosis may be made from a study of the following table in which the symptoms in cases with Flint murmur are placed side by side with those in uncomplicated mitral stenosis and combined mitral stenosis and aortic insufficiency. For the sake of a fairer comparison only those cases of true mitral stenosis and mitral stenosis complicated with aortic insufficiency have been tabulated in which a presystolic murmur was present.

TABLE II.

	Uncomplicated mitral stenosis. (17 cases.)	Mitral stenosis and aortic insufficiency. (14 cases.)	Aortic insufficiency with Flint murmur. (33 cases.)
Small pulse . .	. 82.3 per cent.	28.5 per cent.	.0 per cent.*
Presystolic thrill	. 64.7 "	50 "	42.4 "
Tapping systolic shock	76.4 "	50 "	15.1 "
Valvular first sound	. 64.7 "	78.5 "	30.3 "

* Based upon thirty cases; see above.

These tables bring out certain fairly well-marked clinical differences between the cases of aortic insufficiency with Flint murmur and those complicated with true mitral stenosis. The character of the presystolic murmur is essentially the same in both conditions, with one exception: a Flint murmur is never as rasping and loud as are the more marked murmurs of true mitral stenosis; it is commonly echoing and of moderate intensity. It is fair, however, to remember that in a very large proportion of cases of true mitral stenosis the murmur is also of this same character. Out of the 22 fatal cases of mitral stenosis above referred to the sound was absent or was described as an echo or as a faint rumbling murmur in 12, or 54.5 per cent., of the cases.

The presystolic thrill is also less frequent and less intense, but perhaps the most striking difference between the two conditions is in the character of the systolic shock. In but a very small proportion of the cases of aortic insufficiency with Flint murmur does the apex impulse have the tapping character so significant of a true mitral stenosis; this appears, however, to be present in about half the cases of aortic insufficiency combined with true mitral stenosis. In the majority of instances of Flint murmur the systolic impulse has the usual characteristics of that observed in aortic insufficiency; it is a forcible but rather heaving lift. The snapping valvular first sound is also rare. In the instances with Flint murmur the first sound, if it be not replaced by a systolic murmur, is commonly dull, humming, prolonged, indeed, as is often the case in aortic insufficiency, almost more an impulse than a sound.

But, apart from the physical signs related to the heart itself, there are other points which may be of considerable help in diagnosis. Most important among these is the pulse. The pulse in aortic insufficiency complicated with true mitral stenosis was recorded as small in over a quarter of the cases. In uncomplicated aortic

insufficiency with Flint murmur the pulse is almost always characteristically large and collapsing.

The condition of the peripheral arteries and various points in the history of the case may also be of assistance in diagnosis.

Thus, out of 16 cases of aortic insufficiency complicated with mitral stenosis, in all but 3, or 81.2 per cent., there was a distinct history of rheumatism or chorea, or symptoms justifying a diagnosis of acute endocarditis. In 3 cases the process was clinically arterio-sclerotic.

Out of 33 cases of aortic insufficiency with Flint murmur there was a clinical history of acute rheumatism, or chorea, or signs justifying a diagnosis of endocarditis *intra vitam* in but 13 instances, or 39.3 per cent., while in 18, or 54.5 per cent., there was clinical evidence of a general arterio-sclerosis.

Anatomically the changes in the valves were part of a general arterio-sclerosis or an atheroma of the aorta in 20, or 60.6 per cent., of the cases. In 13, or 39.3 per cent. of the cases, the condition was an acute or chronic endocarditis. In 4 of these cases there existed also arterio-sclerosis.

In 25 cases of uncomplicated aortic insufficiency without Flint murmur the percentages were essentially the same. In 16, or 64 per cent., the process was a part of a general arterio-sclerosis; in 8, or 32 per cent., the condition was due to endocarditis; in 1 the defect in the valve was congenital.

As might be expected, there are certain slight differences in the average age of the cases with Flint murmur and those of aortic insufficiency complicated with mitral stenosis—differences depending clearly upon the fact that, in the one condition, the changes are more commonly due to arterio-sclerosis which is generally a senile change, and in the other to endocarditis which so frequently occurs in early life. This is well shown by the following table:

TABLE III.

Years.	Aortic insufficiency with Flint murmur.	Aortic insufficiency complicated with mitral stenosis.
1–10	1	0
10–20	5	3
20–30	4	3
30–40	9	5
40–50	7	2
50–60	5	2
60–70	1	0
70–80	1	1
Totals	33	16

Thus, it will be seen that 57.5 per cent. of the cases of Flint murmur occurred in individuals under forty years of age, against 68.7 per cent. among the cases of true mitral stenosis. But these differences are too slight to be of any diagnostic importance.

That there is nothing essential in the arterio-sclerotic process which predisposes to the development of a Flint murmur is shown by the fact that out of 32 cases of uncomplicated aortic insufficiency where the lesion was purely arterio-sclerotic in origin, a Flint murmur was heard in 50 per cent., while in 21 instances where the lesions were due to an acute or chronic endocarditis the percentage of Flint murmurs was actually greater, namely, 60.9 per cent.

The diagnostic importance of demonstrable arterio-sclerosis lies in the fact that while arterio-sclerotic cardiac lesions are usually confined to the aortic orifice, in endocarditis, on the other hand, the possibility of simultaneous affection of the mitral valves, and hence the probability of a true stenosis, is appreciably greater.

Broadbent[1] believes the Flint murmur to be more frequent in cases where the insufficiency is combined with stenosis of the aortic valves.

In three of our cases there was aortic stenosis as well as insufficiency, but in only one was a Flint murmur heard. In the other two instances, despite the existence of true mitral stenosis in one, there was no presystolic murmur.

To sum up the results of these comparative observations it may be said that a positive diagnosis of a functional mitral presystolic murmur may be difficult to make. The character of the murmur differs in no way from that of true mitral stenosis. In true mitral stenosis, however, even if complicated with aortic insufficiency, the tapping systolic shock and the snapping first sound are common. The Flint murmur, on the other hand, is usually associated with the characteristic heaving impulse of aortic insufficiency, and the dull, ill-defined, prolonged first sound. A tapping impulse and a snapping first sound, may, however, be present.

Of special importance is the character of the pulse. In cases of aortic insufficiency with Flint murmur the pulse is large and col-

[1] Heart Disease, London, 1900, 8vo., 3d ed., p. 150.

lapsing; in instances combined with true mitral stenosis there is generally an appreciable modification of the size of the pulse.

The diagnosis of Flint murmur is fairly safe when a rumbling or echoing presystolic murmur in the region of the apex is present in aortic insufficiency occurring in an individual with well-marked general arterio-sclerosis, especially where there is no history of any acute malady ordinarily associated with the development of endocarditis, and in the absence of a marked systolic shock or snapping first sound. If, on the other hand, the patient be an individual with soft peripheral arteries and a history of attacks of acute rheumatism or chorea, or other evidences suggestive of the existence of an endocarditis, the probability of concomitant affection of the mitral valve is greater, and the possibility of arriving at a definite diagnosis is correspondingly less.

While, as a rule, the Flint murmur is not of very great intensity, is associated with little or no thrill, with no marked tapping systolic shock, and rarely with a snapping first sound, there may be striking exceptions to this rule. The following case may serve to show how careful one should be in assuming the existence of a true mitral stenosis from the presence of nearly all the classical signs, if aortic insufficiency be present.

D. B., a colored laborer, aged between forty-five and fifty-five years, was admitted to the Johns Hopkins Hospital on July 22, 1896, complaining of shortness of breath and swelling of the legs. His family history was negative, as was his personal history, except for what was, apparently, an attack of sciatica which lasted for about four months.

For several months before entry he had been suffering with shortness of breath, which had steadily increased. For four weeks there had been swelling of the abdomen. Two months before entry he had to give up work on account of shortness of breath.

Physical Examination. The patient was a fairly well-nourished colored man with well-marked arcus senilis. The radial arteries were moderately thickened. There was edema of the legs and ascites. Examination of the lungs showed fine moist râles at both bases.

Heart. The cardiac impulse was in the fifth interspace about in the mammillary line. There was no marked systolic shock, but a slight presystolic thrill was to be felt. On auscultation at the apex there was heard a slight presystolic murmur ending in a snapping first sound, followed by a soft systolic murmur; the second sound was not audible at the apex. Passing upward toward the base a well-marked diastolic murmur of aortic character

became audible. It was of maximum intensity at the left third and fourth cartilages. The pulse was collapsing.

Under rest, diuretics, and potassium iodid the patient improved greatly, and left the hospital on August 31st.

From this time up to the date of his death the patient was admitted to the hospital five times.

On September 21, 1896, the following note was made by Professor Osler: "At the apex-beat a loud systolic shock is preceded by a somewhat rough murmur in diastole, which does not run quite up to the beat."

And, again, on September 25, 1896: "At the sixth interspace a rough presystolic murmur is well heard, and the shock of the first well felt; no thrill. The systolic shock is marked."

On October 2d: "The shock of the first sound is well marked on palpation."

On April 2, 1897, the following note was made by Dr. Thayer: "The pulse is collapsing and rather large, but not as large as often seen in aortic insufficiency. At the point of maximum impulse there is no distinct thrill. The first sound is rather sharp and followed by a slight systolic murmur which is lost in the mid-axilla. As one passes outside the point of maximum impulse the snapping character of the first sound is rather suggestive. The second sound at the point of maximum impulse is followed by a slight, soft, diastolic murmur. Almost immediately after the second sound there begins another murmur, which at first is extremely difficult to separate from the aortic diastolic, but which is of a different pitch. This is heard best in the fifth space just in the mammillary line, where it has an echoing quality and increases in intensity, ending in the first sound. It is not heard above the fifth rib or inside the parasternal line, and is lost a short distance outside the point of maximum impulse. Above and inside this area a soft systolic and diastolic murmur are to be heard. The diastolic murmur is audible in the aortic area, but is loudest along the left border of the sternum at about the fourth space; it has a soft aortic character. In the aortic area it does not entirely replace the second sound. The second pulmonic is not particularly loud; systolic and diastolic tone in the carotids."

April 9, 1897, Dr. Osler: "Systolic shock is well felt at the apex and base. . . . The presystolic murmur has all the characters of a true stenotic murmur."

The patient died on October 30, 1898. Repeated notes were made by Professor Osler, by Drs. McCrae and Futcher, and by myself. The valvular snapping character of the first sound was constantly referred to. The thrill was of moderate intensity and was often absent. The presystolic murmur also varied greatly in intensity.

Owing to the nature of the systolic shock and the snapping character of the first sound, a diagnosis of true mitral stenosis in association with aortic insufficiency was universally concurred in.

The necropsy, however, showed general arterio-sclerosis with moderate

thickening and retraction of the aortic valves. The mitral curtains were absolutely normal.

A word before closing as to the cause of this interesting phenomenon. As stated in the beginning, Flint[1] assumed that the back-flow of blood from the aorta resulted in a floating upward of the valvular curtains so that they were brought approximately into apposition, thus causing a practical stenosis of the mitral valve at the time of contraction of the auricle.

Keyt's[2] view that the murmur arises at the aortic orifice in systole is scarcely worth considering.

Guitéras,[3] as has been said, adopted a modification of Flint's view. "He forgets, it seems to me," he says, "that in aortic regurgitation the leaflets are not floated upward, but are actively driven against the auricular blood by the force of the general arterial tension. . . . I maintain that these propagated murmurs are, in fact, mitral obstructive murmurs, and that they are more apt to develop when the posterior aortic segment is affected, because in such cases the recurrent stream is brought to bear directly against the anterior leaflet of the mitral valve."

Sansom[4] asserts that the development of a presystolic murmur would be impossible if, as Flint suggested, the mitral curtains were actually brought into coaptation. I cannot imagine that, the mitral curtains being brought into coaptation, and the orifice being itself closed, any force proceeding from the auricle could separate them or cause the blubbering sound. It would be quite otherwise, however, if they were brought together without completely closing the auriculo-ventricular aperture. In such a case two explanations will be possible.

(*a*) The lifting force of the current impinging upon the under surface of the great anterior mitral curtains might so obstruct the current from the auricle as to create a *de facto* impediment at the end of each disastole; or

(*b*) The vibrations might be directly communicated by the regurgitant stream from the aorta to the great mitral curtain. The nearness of the posterior segment of the aortic valve—diseased,

[1] Op. cit. [2] Op. cit. [3] Op. cit.
[4] The Diagnosis of Diseases of the Heart and Thoracic Aorta, London, 1892, p. 385.

perhaps, so that the morbidly-produced orifice in diastole presents ragged or fringed borders—to this mitral flap may well account for such vibrations. These vibrations may attain only to an intensity and rapidity sufficient to cause murmur somewhat late in the diastolic period. The force of the auricular systole would necessarily amplify and intensify such vibrations of the free edge of the flap until the commencement of ventricular systole or the tug of the chordæ tendinæ abruptly stopped them, bringing both curtains of the valve together and completely closing the auriculo-ventricular orifice.

It occurs to me that this is a more probable explanation than that which postulates the production of a virtual stenosis of the orifice by the fluid pressure of the aortic regurgitant stream.

Potain[1] is inclined to accept the idea that "the retrograde blood current from the aortic orifice which is insufficient, presses back the great curtain of the mitral, whence a relative narrowing of the mitral orifice. This great curtain is then between two parallel currents of varying rapidity, the retrograde current of aortic insufficiency and that produced by the blood coming from the auricle. Under the influence of these two currents the mitral valve enters into vibration, which results in the production of a thrill appreciable by the hand and of the presystolic murmur or rumble perceptible to the ear."

Essentially the same view is held by Broadbent.[2]

This explanation of the origin of the murmur is similar to that of Guitéras, and would seem, upon the whole, reasonable.

In conclusion, one may be justified in saying that in uncomplicated aortic insufficiency a rumbling, echoing, presystolic or mid-diastolic murmur limited to the region of the apex of the heart is very common, occurring, when carefully looked for, in fully half of the cases. The characters of this murmur are in no way different from those commonly observed in true mitral stenosis, with the exception of the fact that it is usually of moderate intensity. It is, however, rarely associated with a tapping systolic impulse and a snapping first sound, which are the rule in true mitral obstruction, while the pulse is large and characteristic of uncomplicated aortic insufficiency

[1] Gaz. d. Hôp., Paris, 1893, lxvi. 295. [2] Op. cit.

In the absence of these signs and with a large pulse, the functional character of an apex presystolic murmur in aortic insufficiency is to be suspected, especially in cases where there is no history of acute infectious processes such as are ordinarily associated with endocarditis, and where there is evidence of well-marked arterio-sclerosis.

A Flint murmur may, however, be associated with many of the clinical features of a true organic mitral obstruction.

DISCUSSION.

DR. CABOT: At the Massachusetts Hospital, among the postmortem records there are ten cases in which a normal mitral valve has been found, with a regurgitation at the aortic, and in which the clinical diagnosis had been mitral stenosis. The details practically confirm all that Dr. Thayer has said. Five were under forty years of age, and five were over forty. There was history of rheumatism or chorea in only two; the symptoms of pulmonary congestion were marked in six; the tapping first sound was noted in only one; in four the thrill was marked.

In the last ninety-one cases of aortic regurgitation I have examined, using the same criteria which Dr. Thayer has presented for the identification of Flint's murmur, it has seemed to me to be present in fifty.

DR. TYSON: A case now under my observation in the Philadelphia Hospital would seem to fulfil the requirements of a Flint murmur in a striking manner. There are present all the signs of aortic regurgitation, with, however, the absence of a diastolic murmur, or at least an easily recognizable diastolic murmur. I have not been able to hear it in this case, though others who have listened to the heart say they can hear a feeble diastolic murmur at the usual site of aortic regurgitant murmurs. Associated with it, however, are all the other signs of aortic incompetency, including a high degree of hypertrophy of the left ventricle, a Corrigan pulse, a capillary pulse, and a presystolic murmur, which further corresponds with the Flint murmur as described by Dr. Thayer in that it has less intensity than the presystolic murmur associated with mitral stenosis.

GRANULAR DEGENERATION OF THE ERYTHROCYTE.

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Granular, basic, or punctate degeneration of the erythrocyte is a condition in which this cell presents fine or coarse granules that have an affinity for basic stains. This degeneration affects cells which show other evidences of pathologic change, as poikilocytosis and polychromatophilia, or may be present in a cell which in all other appearances is normal. Further, it may be seen in nucleated erythrocytes, where it shows absolutely no relation to the nucleus. In size the granules may be so small that they can scarcely be seen, or so large as to be nearly the size of the eosinophile granule. The shape is usually rounded, though pear-shaped, and, exceptionally, rod forms are encountered. Cells may show one or the other sized granules, or a mixture of both. The granules are usually equally distributed throughout, or small clumps may be seen in different parts of the cell. This latter arrangement is especially marked in the early stages of experimental productions and is rare in blood from the human subject. There may be a few large or fine granules scattered in the cell, or countless numbers densely packing the cell and to a great extent obscuring the intergranular substance.

It is impossible to detect this form of degeneration either in the fresh blood or in dried and unstained mounts.

Attention has been called to these granules as a special form of degeneration only in the past few years. Their presence in the circulating peripheral blood had been undoubtedly observed for a much longer period. The earlier writers, Geelmyden, Hausemann, V. Noorden, Loos, Askanazy, Shuman, Lazarus, Klein, Zenomi, and Lenoble

observed such granules; and lately Litten, Krause, Bouchart, and Grawitz (in his first publications) called attention to cells with minute basic granules, which they thought were products of fragmentation (karyorrhexis) of the erythroblast, and, indeed, this view has not been wholly abandoned at the present date. Others have confounded them with polychromatophilic changes, and Plehn considered them related to malaria.

Grawitz, in his paper of September, 1899, was the first to lay particular stress on this granulated cell as an evidence of a special form of degeneration, and he opposed the earlier view of fragmentation or persistence of remnants of the nucleus, and pointed out that in his observations these cells were found in blood in which there was no other evidence of cellular change, and in which there were no nucleated erythrocytes; and, further, that when nucleated cells were present there were no transitional stages. Later, he demonstrated that this degeneration could be seen in nucleated cells while the nucleus was intact. In further studying the cells of the blood-forming organs he was unable to find this change in the newly-formed cells or in the erythroblasts, and, therefore, came to the conclusion that this degeneration was probably of peripheral origin, and he suggested that it was possibly due to the direct action of some blood poison. Litten substantiated this view in the study of the bone-marrow in cases of severe anemias, where he found much evidence of erythrocytic degeneration, but was unable to find evidence of this special granulation. On the other hand, both Pappenheim and C. S. Engel have seen similar granules in embryonal blood. Hamel and Behrendt were the first to demonstrate the frequency of this cellular change in the peripheral blood of patients poisoned by lead. These observations gave Grawitz support for his former theories regarding their origin, and led him to study the blood under experimental intoxications with this metal. Experimentally he was able to observe these granulated cells in the blood of mice at a very early stage of the intoxication, and even when these animals had been subjected to the minute dose of 0.03 gramme of the acetate of lead for a very short time. Moritz repeated similar experiments, using rabbits, and clearly demonstrated to his own mind that these granulations are an evidence of a true degeneration and not artefacts.

Sabrazès, Bourret, and Léger claim to have first produced these granules experimentally in animals, using guinea-pigs and injecting small doses intraperitoneally.

Grawitz, working upon a theory suggested by Plehn's observation of similar granulations in the blood of Europeans coming to the tropics,

thought that the change of temperature had something to do with their formation. Following this idea, he was able to demonstrate the presence of these granules in mice subjected to increasing daily temperatures.

Schur and Loewy, in an extensive study of the bone-marrow in various diseased conditions, were unable to find such granulations. They came rather hastily to the conclusion, therefore, that this cellular condition was of artificial production.

From the foregoing observations and experimental studies it seems to us without a doubt that these granular formations, be they the remains of fragmentation of a previously existing nucleus or a special production, are an evidence of a pathologic change when found in the circulation. With this in mind we have undertaken the study of this granular degeneration in lead workers and experimentally in its relations to lead intoxications. Our studies have included:

1. Cases of chronic lead-poisoning.
2. Studies in lead workers with no subjective symptoms.
3. Heat cases—heat workers and local therapeutic heat applications.
4. Results of experiments.

1. *The Cases of Chronic Lead Intoxication.* In all the cases so far reported by Hamel, Behrendt, Grawitz, Moritz, etc., in which the granules have been sought they have invariably been found. This granular formation seems to be a very early evidence of lead intoxication; in fact, as will be seen later, appearing before all other symptoms, considered subjectively or objectively. The number of granular cells appears to be in direct proportion to the severity of the poisoning, and their disappearance is noted as the symptoms ameliorate.

Four of our cases were hospital cases, the men coming under observation with marked and typical symptoms of chronic poisoning. The granules were present in all four cases in varying numbers up to nine in one field (of a very thin spread and $\frac{1}{12}$ oil immersion). The granules varied in size, some cells showing very fine and others very coarse granules, and others a mixture of both. It might be said that in the severest cases the coarser granules are slightly in excess.

The blood otherwise showed only very slight changes from normal, namely, a slight paleness of the erythrocytes, and a slight poikilocytosis, especially marked in irregularity of size. A very few nucleated erythrocytes were seen. These were normoblasts, and the majority of them showed the granular degeneration of their protoplasm while the nuclei were intact as far as could be detected.

2. *Lead Workers Without Subjective Symptoms.* Grawitz and Moritz each had five cases which could be included under this head, and in

which they found granules. Examining twenty-one lead workers without subjective symptoms we found the granules present in every case. The spreads of blood were taken at the workshop while the men were actually engaged at their various duties. The nature of the work of these men included that of foreman of the works, "sprinklers" who watered the dust, and laborers, some handling the metallic lead, others the oxide, others the "wet pulp." These men were more or less exposed to the dust of lead during their working hours.

The list includes two who had worked only four days, the shortest exposure, and one man who had been constantly working in the metal for twenty-four years, the longest exposure. Only one of the twenty-one men, an oxide worker, had presented symptoms. This one had had several distinct attacks of chronic lead-poisoning in ten years of actual contact with the metal. One other, who had been working only three months, and who showed the greatest number of granules in the stained spread, had had about one month previous to observation an indefinite illness which had detained him one week from his work. The number of these granulated cells varied from a few in a spread to as many as two or three in a field of the microscope. The other evidences of blood changes were only slight and rather inconstant as to any particular form of variation. Twelve cases showed slight poikilocytosis, but more particularly irregularity in size of the corpuscles. Two at least certainly had deficient hemoglobin (noted by the lack of stain taken by the cell). Three showed only a slight polychromatophilia, and in five cases normoblasts were observed, most of these latter cells showing granules in their protoplasm while the nucleus was unchanged. (See table at end of article.)

3. *Heat Cases.* The studies we made in this line were suggested by Grawitz's experiments with mice and by Plehn's observation on Europeans coming to the tropics, and by a case of an iron worker in whose blood we had found granulated cells in large numbers. They consisted in studying the blood of four iron workers who were subjected to intense heat while at their work at furnaces, and that of patients using local dry hot air treatment. In these latter cases, of which there were four, the various parts of the body, especially the limbs, were subjected to a temperature of 300° F. In the former as well as in the latter cases we were unable to find a single granulated cell in the spreads made from the peripheral circulation.

In the case above mentioned we were led to conclude that the granules were the result of the chronic diarrhea which had existed for twenty years, or were possibly due to lead which he not unlikely received dur-

ing a prolonged course of treatment. Here we might include five cases which had been subjected to applications of lead-water and laudanum. In two of these cases the application had been made to denuded areas, while in the remaining three to the unbroken skin. Daily observations were made in these cases for a week or ten days, but in them we were unable to find any evidence of granular degeneration.

4. *The Experimental Study.* These granules have been produced in mice by Grawitz, in rabbits by Moritz, and also in guinea-pigs and pigeons by Sabrazès, Bourret, and Léger.

In our own cases dogs were used, and the lead acetate was administered by mouth in capsules with the food. The initial dose was always a gram, irrespective of the animal's weight. In two dogs one gram was given daily throughout the observation; in three the initial dose of one gram was increased by one gram each day until the experiment was concluded. The blood in all these cases was carefully studied for several days previous to the experiment, and then every twenty-four hours for a few days after the intoxication had begun, and then at longer intervals. Spreads were made from the carefully shaven and cleaned ear, dried for twenty-four hours, and then fixed by heat, and studied under various stains.

Distinct granules appeared after the initial dose, usually in about three days, irrespective of the size of the dose compared to the animal's weight, or to the manner of increase of the same, though indistinct granules were noted after twenty-four hours. In the three cases in which the dose was rapidly increased the granules became more numerous in a shorter time than when the gram dose was given daily. In all of these cases the early granules showed a greater tendency to cling together than they did later. This clinging together or clumping of the granules in different parts of the cell was more or less characteristic in these experimental productions. It was usually absent in the cases of lead-poisoning or of the lead workers. On the other hand, the even distribution so commonly seen in the lead workers was not observed at any stage of the experimentally produced poisonings. In the dogs it was a common observation to find associated with these granulated cells erythroblasts and polychromatophilia. The finding of these latter types of blood degeneration does not seem to us to be of such significance as when they are found in the human subject. They are a rather frequent finding in dogs which are used for experimental purposes. The appearance of granular degeneration in the peripheral blood, twenty-five hours after one of the writers had taken seven and one-half grains of lead acetate, shows conclusively the early production of this change in human blood.

The fact that these granules were not found in the bone-marrow by the various observers led us to believe with Grawitz that they were of peripheral origin, or that the usual methods for fixing the bone-marrow were inadequate for their demonstration. To determine the former view blood was taken from various veins of the body, stomach, mesentery, liver, portal vein, spleen, and heart in animals killed for this study, and compared with the blood taken ante-mortem from the ear. The results of these observations were as follows: The blood taken from the portal vein and splenic vein showed a greater number of these granules than did the blood of the ear, heart, or mesenteric vessels. This was but an isolated observation, and we hesitate to draw any definite conclusions. In five later cases this unequal distribution was not sufficiently marked to prove the peripheral origin of these granules.

For the study of the bone-marrow two methods were used. The bone was sectioned in pieces, three-quarters of an inch long, and the marrow was taken from its bony case by running an ordinary sewing needle around it, then, when it was freed from the bone, carefully pushing it out. In this way the marrow was obtained intact. Spreads were made from this marrow by the usual methods for making blood smears. Some of these spreads were fixed immediately in ether and absolute alcohol; absolute alcohol; 10 per cent. formol; saturated aqueous solution of mercuric bichlorid; 1 per cent. osmic acid; saturated solution of picric acid in absolute alcohol; others were dried and fixed with heat alone, or previously to heating treated with ether to remove the fat. Further, this shelled-out bone-marrow was fixed by the usual methods and sections made from paraffin blocks. From the former spread specimens, variously fixed, we were able to demonstrate the granular changes in the erythrocytes and the erythroblasts, but in no bone-marrow spread was the number of these granules in greater number than we found in the peripheral circulation. These cells may have been in the circulation of the bone-marrow. The fixing agents from which the best results were obtained were ether and absolute alcohol, absolute alcohol, and bichlorid solution. From the great amount of fat which is always present in these spreads, and which interferes to a great extent with fixing the specimens by the usual heat method, it was thought that it might interfere with the staining of these granules. To ascertain the rôle which fat played in this way spreads from the ear blood were kept at 52° C. for twenty-four hours on fat taken from the mesentery of a dog. They were then fixed by heat and stained in the usual way. While the granules could be found

after the spreads were so treated there seemed a decrease in their number, especially so in the case of the finer granules.

From the bone-marrow fixed in the various methods and mounted in paraffin sections were cut at 2 μ. In these sections fixed by various agents—alcohol and ether; absolute alcohol; osmic acid, 1 per cent.; formol, 10 per cent.; Müller-formol; Zenker's solution; Flemming's fluid—we were unable to demonstrate the presence of granules.

In our routine study of these granulated cells all the blood spreads have been fixed by heat on a copper plate. The specimens heated for a few minutes only seem to be better prepared for staining than those heated for a longer time. The stains used for this work have been the usual hematoxylin and eosin stains and thionin pheniqué. In using the former stains the specimens should be overstained with hematoxylin; with the latter the granulated cells stain rapidly and are very easily detected.

With aqueous solutions of the following stains we have been able to detect these granules in specimens fixed by heat: basic fuchsin, carbol-thionin, anilin green, gentian violet, Bismarck brown, tuloidin-blue, dahlia, methylene-blue; also Löffler's methylene-blue, hematoxylin, hemalaum. We have been unable to find them when we used aqueous solutions of anilin blue, Berlin blue, iodin-green, indulin, tropeolin, blue-black, methylene-green, orange G., acid fuchsin, rosin, Ehrlich triacid, nile blue, benzopurpin. For routine work we recommend the use of the usual hematoxylin and eosin stains, or, which is especially good for the study of these granules, the thionin pheniqué, the formula of which is:

Thionin (French)	0.05
Carbolic acid	1.00
Alcohol 95 per cent.	10.00
Aq. destil.	90.00

The stain becomes better with age.

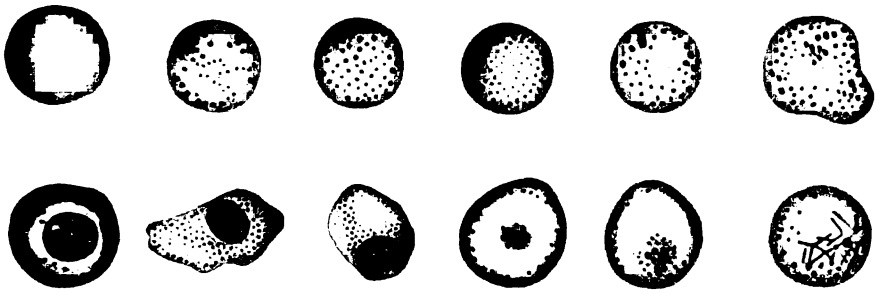
Our conclusions are:

1. The granules are a constant finding in cases of lead-poisoning, and appear very early in cases under the influence of lead salts long before subjective or other objective symptoms can be demonstrated.

2. The granules disappear in cases of chronic lead-poisoning as the convalescence is established.

3. Apparently lead does not produce an immunity, as one of the cases worked for twenty-four years, another for twenty years, without having pronounced symptoms of lead-poisoning, and in both of these cases the granules were present in moderate numbers.

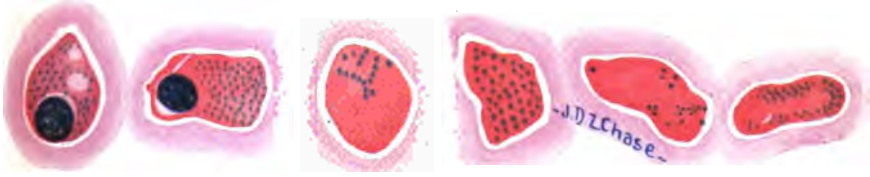
Lead Workers.



Dog's Blood.

Lead Poisoning.

Bone Marrow.



STAINS.—Nos. I., II., and IV., Eosin and Hæmatoxylin. No. III., Thionin Phenique.

4. The granules may be produced experimentally in dogs, appearing in a very few days after the beginning of the experiment, and increasing as the intoxication becomes severe.

5. The granules in the experimental cases are rather fine, and show a tendency to clump at first; later all varieties appear.

6. We believe these granules to be a true degeneration of the erythrocyte and having no relation to nuclear fragmentation or to polychromatophilia.

LEAD WORKERS.

Case No.	Time worked in lead.	Degree of exposure.	Poikilocytosis.	Hemoglobin estimated by the amount of stain per cell.	Nucleated erythrocytes.	Granular degeneration.	Estimated average number of granular cells to a field ($^1/_{12}$ oil immersion).
1	7 years	Considerable.	Slight.	Normal.	Present (one in slide).	Present.	One to two cells to a field.
2	5 "	Moderate.	"	"	Absent.	"	One cell to every two or three fields
3	3½ "	Considerable.	"	"	Present (few).	"	One cell to every four or five fields.
4	24 "	Constant.	"	"	Absent.	"	One cell to every three or four fields.
5	7 "	Considerable; poisoning 5 yrs. ago.	Absent.	"	"	"	One cell to every ten or twelve fields.
6	9 "	Slight.	"	"	"	"	One cell to every ten or twelve fields.
7	11 "	Considerable.	Slight.	Reduced.	"	"	One cell to every ten or twelve fields.
8	9 "	"	Absent.	Normal.	"	"	One cell to every seven or eight fields.
9	7 "	"	"	"	"	"	One cell to every four or five fields.
10	2 wks.	"	"	"	"	"	One cell to every six or seven fields.
11	6 "	Constant.	Slight.	Reduced, and polychromatophilia.	Present (many).	"	One cell to every six or seven fields.
12	8 mos.	"	"	"	Present (few).	"	One cell to every six or seven fields.
13	3 "	"	"	"	Present (many).	"	Two to three cells to every field.
14	4 days.	"	Absent.	Normal.	Absent.	"	One cell to every four or five fields.
15	4 "	"	"	"	"	"	One cell to every four or five fields.
16	5 years	Considerable.	Slight.	"	"	"	One cell to every field.
17	1 year	"	Absent.	"	"	"	One cell to every four or five fields.
18	2 wks.	"	"	"	"	"	One cell to every two or three fields.
19	4 "	Constant.	Slight.	"	"	"	One cell to every three or four fields.
20	20 years	Considerable.	Absent.	Reduced.	"	"	One cell to each field.
21	10 "	"	Slight.	Normal.	"	"	One cell to every three or four fields.

DISCUSSION.

DR. JACOBI: I rise to ask a question. The doctor has spoken of lead-poisoning, and at the same time he told us that a large number of the men examined showed no symptoms of any illness, but had these same granules in the blood cells. Now, what influence has this condition of the blood on the general condition of the individual? We certainly could not speak of poisoning unless there were some symptoms that could be recognized.

DR. STEWART: One of the first symptoms of lead-poisoning is an anemia, and it seems that, finding this condition in connection with this degeneration, we might call the condition a poisoning. It would become a matter of diagnostic importance.

DR. JACOBI: I cannot say that I find that answer quite satisfactory. We have been told that the patients were quite well, and in spite of that these changes in the blood were found. If it is so easy to influence the blood by lead, we must be guarded in our therapeutic measures as to the doses we are permitted to give. That is why I asked the question. I now and then give in hemoptysis very large doses of lead, and find that these so-called large doses—twenty to forty grains or more a day for successive days—will stop a very bad hemorrhage when the diminutive doses of the books would have no effect whatever. How am I justified in giving such doses?

DR. PEABODY: I have myself produced a typical lead-poisoning by giving five grains of the acetate three times a day for four days in succession. I am quite well aware that the text-books say that lead colic is not producible in this way, but it is surely a mistake. It may often be given for prolonged periods without bad results, but poisoning can occur.

DR. STEWART: With all due deference to Dr. Jacobi, I must say I think it is dangerous to give such large doses.

DR. STENGEL: I have no desire to enter the field of discussion as to when an innocuous body becomes an intoxicant. I believe that many of us are developing arteriosclerosis without showing the acuter symptoms of our abuses. In the same way many of those men working in lead factories who are to all appearances in perfect health are still the subjects of lead-poisoning. I did not say they had no lead-poisoning; they did have, but they had none of the usual symptoms of that condition. The marked changes in the blood were found, but the colic and nervous symptoms were absent.

OBSERVATIONS ON THE NATURE AND TREATMENT OF PERNICIOUS ANEMIA.

By ALEXANDER McPHEDRAN, M.B.,
OF TORONTO, CANADA.

Many causes and conditions have been adduced to account for the occurrence of pernicious anemia, but none of them is satisfactory—nothing definite is known as to the actual cause. This unknown factor is generally believed to be a toxin; on this theory only can the phenomena be accounted for. Among the English-speaking profession generally the toxin is looked upon as of gastrointestinal origin, and that it acts on the blood of the portal system especially, causing rapid hemolysis, and that the other effects produced are secondary, developing in the course of the disease. Many German physicians, on the other hand, refer the disease to a toxin affecting hemogenesis, as shown by the abundance of myeloblasts in the bone-marrow and in the blood, indicating a reversion to the embryonal type.

It is probable that both views are in part correct; that not only blood destruction but blood formation has been effected by a common toxemia resulting in the genesis of abnormal corpuscles and the rapid destruction of the less resistant ones. The blood formation is atypical, and, therefore, to be attributed to pathologic irritation rather than to excessive physiologic stimulation.

The other changes met with, especially those in the spinal cord and peripheral nerves, are probably produced by the action of the same irritant rather than as the result of the protracted anemia.

The irregular course of the disease with its remissions and exacerbations, its irregular fever, the frequent disturbance of the mental condition, and the occurrence from time to time of vomiting and diarrhea, all indicate a common toxic cause.

The fact that the general condition does not bear a definite relationship to the blood state goes to show that there is something else than the poverty in corpuscles on which it depends. This is well illustrated by the contrast between the condition of a miller who was able to do, without difficulty, all but the heaviest work of his mill, and yet his blood only had 1,000,000 red corpuscles per c.mm., and that of a physician with over 4,000,000 corpuscles whose case is given in detail below under the head of treatment. In the case of a member of the Canadian House of Commons during the past year there has never been more than 3,500,000 red corpuscles per c.mm., and yet he has not only regularly and with marked ability attended to his duties in the House, but has also conducted a most vigorous election campaign without either detriment or exhaustion. It is to be noted that in these, as in all cases during well-marked remissions, the color-index is always near the normal, and that the corpuscles show less deformity and there are fewer nucleated ones among them.

That the condition is a toxemia is further indicated by the early occurrence of marked weakness. This, in most cases, is the first symptom, and it may be complained of a considerable time before the pallor is observed. It must, therefore, be independent of the anemia to which, as already stated, it is not proportional. In twenty-two cases observed during the last three years, with scarcely an exception the first deviation from health noticed was the weakness; pallor followed soon afterward.

It is to be observed, also, that the early occurrence of weakness before, as a rule, any disturbance of the digestive tract is noted does not support the theory that the toxin is of gastroenteric origin, or that the digestive tract is the site of infection, but rather indicates that the changes in it are secondary to the toxemia. The disturbances of the stomach and bowels doubtless, however, increase the toxemia and, therefore, aggravate the condition.

The grounds for the opinion that the toxin is of gastroenteric origin is the constancy with which disease or disturbance of the function of the digestive tract occurs. Few if any cases are met with in which there is not at some time a history of diarrhea and vomiting. In my twenty-two cases diarrhea and vomiting occurred practically in all of them at some period of the disease, usually

early, but sometimes later. But the postmortem conditions found in the relatively few cases examined do not afford much support to the theory, as in most of them all that has been found is atrophy of the gastric mucosa. Atrophy, however, occurs in gastric carcinoma and many other conditions which have shown no signs of pernicious anemia, and then there is wanting evidence that the atrophy is not a late change in the disease. The only evidence of its early occurrence is the absence of free HCl from the gastric secretion, but free HCl is temporarily and occasionally permanently absent in many other conditions. During the remissions in pernicious anemia the appetite and digestion are often quite vigorous, and a full diet may be as well disposed of as in health. At such times there is every evidence of a secretion of HCl. Even in malignant pyloric obstruction HCl may be restored to the secretion after the condition has been relieved by gastroenterostomy. Of late much importance has been attached to the probability of infection of the stomach by secretion from diseased gums around decayed teeth.[1] There is no doubt that such unhealthful conditions of the mouth may cause gastric catarrh, but that is far from proving it even indirectly a cause of pernicious anemia. It is a question whether decayed teeth and diseased gums are found to exist in pernicious anemia in a greater proportion of cases than in other chronic exhausting diseases. There is such a vast army of people whose teeth are decayed and gums unhealthy that it would require a marked connection between the condition of the mouth and any constitutional disease to establish a relationship of cause and effect even in a remote degree. In my twenty-two cases I have notes of the condition of the mouth in seventeen. One or more teeth were carious in ten of these, but nearly all of them were too well cared for to be a possible source of infection of the stomach. In only four of these cases were the gums unhealthy, three of them being only slightly affected, and the fourth only fairly severely. In none was there a purulent secretion. It is further to be observed that these cases were not more affected by stomatitis or gastrointestinal disturbances than were those whose teeth and gums were perfectly healthy.

[1] William Hunter, Medical Press and Circular, April 3, 1901, p. 353.

One case, at present showing very grave symptoms of pernicious anemia, was under treatment for two years for dilatation and prolapse of the stomach, with marked disturbance of its function. She was then quite thin and anemic, but the blood did not present the characters of pernicious anemia, and she made a very good recovery. Her present illness began during the past winter.

There was a history of pernicious anemia in the family of two of my cases. One of them, a young man, whose death is just reported, had a brother who died of the same disease about four years ago. The history was typical, so that there can be no doubt as to the diagnosis. The other case is that of a lady, aged about seventy years. She has been ailing for nearly two years, and presents characteristic symptoms in a marked degree. Two of her brothers died a few years ago of a disease with similar symptoms and history.

Symptoms of the disease of the nervous system occurred in nine of the twenty-two cases. In most of them there were only slight feelings of numbness in the extremities—the hands chiefly. In the case of Dr. J. E. E., not only the numbness, but ataxia was quite marked, and the mind was not quite vigorous and clear even during his remissions, in some of which he was almost well.

In a lady, aged sixty-eight years, there was a sensation of extreme coldness in the hands that was distressingly painful at times. Her numbness was also marked. Severe neuralgia of the head in all parts, but usually affecting one side more than the other, was the form the nerve symptoms took in a young woman. The pain could scarcely be relieved until a remission of all the symptoms occurred, when she recovered fair health for a time; a relapse followed, and terminated fatally six months later.

Of the twenty-two cases sixteen were males—an unusually large proportion. They were from all walks in life, but none was subject to undue privation or was burdened with excessive work or "carking care." In no case was any apparent cause evident.

In estimating the value of the treatment in any disease it is necessary to take due account of its natural course. This is especially true of pernicious anemia, whose course is subject to such sudden and extreme changes. There are few diseases in which more marked remissions occur. It is not unusual for cases almost moribund to be about in a few days and resume work in a few weeks. This

was the history in a man last year. He had been ailing for some months, and in April was so prostrated that he could not be roused; blood-stained fluid flowed from his mouth, saturating his pillow; yet in a few days he was sitting up, and returned to his home within a week, a distance of 100 miles. During the summer he considered himself well, and worked at his trade as a stone-mason. He relapsed in the autumn, and spent the winter indoors, with hopes of improving with the advent of warm weather; but he grew worse rather suddenly, and died in April last.

Another man, under my care at the same time, in his first attack two years before was so prostrated that his physician told him he would not be able to return to his office for a year; but he was there in two weeks, and continued well, as he thought, for a year, when he relapsed, failing steadily, with the usual exacerbations and remissions, until he died six months later.

Such cases as these show the inappropriateness of the name "progressive" pernicious anemia. The disease is remittent, not *progressive.* Many run a milder and more persistent course, but in these, also, remissions occur, and from time to time give promise of recovery. As in the case of the member of the House of Commons already referred to, the recovery may be almost complete and remain unchanged for a year or more; but examination of the blood always shows some characteristic deviations, and a relapse may be confidently expected sooner or later. This has been my experience with the twenty-two cases observed during the last three years. Of these fourteen have died, four are running the usual variable course, and the remaining four have not been heard from for some time.

Arsenic, since its introduction by Bramwell, has, until recently, been regarded as a specific in pernicious anemia. As the natural history of the disease has become better understood confidence in it has gradually lessened, until now many regard it as of little value. The only case of complete recovery I have had was apparently due to its action.[1] The case was that of a physician who, in 1889, presented all the phenomena of pernicious anemia with acute symptoms. The red corpuscles were reduced to 750,000 per c.mm., and there was marked poikilocytosis, with much variety in size. Histo-

[1] Medical News, Philadelphia, 1890, p. 367.

logic examination of the blood was not then further made. He took arsenic very freely for three months, causing considerable peripheral neuritis. His recovery was complete, and he has since remained well. In the light of my more recent experience I am inclined to doubt the diagnosis, although it is not apparent wherein the error lies. In none of my late cases has arsenic proved of any service. In many of them it soon caused gastric irritation, and had to be discontinued.

The general acceptance of the theory of gastrointestinal toxemia has naturally led to the use of various antiseptics. Of these mercuric bichlorid has been most generally used, both locally as a mouth-wash as well as internally. My experience with it has unfortunately not been satisfactory; no tangible good has resulted from its use. The use of other antiseptics, as salol, resorcin, creasote, bismuth salicylate, and bismuth naphtolate, have all been equally ineffective. Should this plan of treatment after due trial prove unavailing it will go far to show that the theory of the origin of the disease from a gastrointestinal toxin is incorrect.

With a view of supplying the blood with an artificial serum and stimulating lymphagogue action and excretion of toxin by the kidney, I have given normal saline subcutaneously in a few cases. I first gave it to an old man in the Toronto General Hospital, who was so prostrated as to be almost unconscious. After the first injection of a pint he roused up and remained much better. A pint was given every second day, and on the alternate days the same amount was given by the rectum. The subcutaneous injection was so painful that he declined to continue its use, and the saline enemata soon caused diarrhea, and had, therefore, to be stopped. He improved very much, and left the hospital in very fair condition, with over 3,500,000 corpuscles per c.mm. He returned four months later in a relapse, and died in a few days. In a few other cases improvement followed the subcutaneous saline, and in one there was apparently a recovery, but he may have relapsed, as he has not been heard of for some time. It is, unfortunately, too painful for most people to endure. The rectal administration should be as effective, but it cannot be continued on account of the diarrhea. If, as Rumpf has lately pointed out, there is, in addition to the hydremic state of the blood, an excessive quantity of sodium chlorid present,

it would seem injudicious to add more water and NaCl to blood already surcharged with these constituents. However, if the solution stimulates the renal secretion its use may so increase elimination from the blood as to more than counterbalance the evil effects of the introduction of more NaCl and water into the blood.[1]

The use of various other sera is illustrated by the history of the case of Dr. J. E. E. He was fifty years of age, and practised in a neighboring city. Symptoms of weakness were noticed early in 1899, and pallor shortly afterward. His teeth and gums were very healthy, but he suffered much from stomatitis, especially when his stomach was disturbed, as it was frequently. He could take arsenic only for a few days, as it caused nausea and vomiting, and normal saline by the bowel set up diarrhea. Mercuric bichlorid was used for some time, both locally for the mouth and internally for the general toxic condition, without doing any appreciable good. Bismuth salicylate and similar antiseptics were given from time to time for the diarrhea, which always recurred when the stomach was disturbed. His history was the usual one of mild exacerbations and remissions. He had a severe urticaria. This was also the result of its use in three other cases. Then antidiphtheritic serum was used, 2 c.c. being given every second day. Its use in two previous cases was followed by gratifying results, doubtless *post hoc* rather than *propter hoc*. They were both old men, and one of them died the following year of acute diarrhea; the other two years later of senility. In Dr. E.'s case the serum had no apparent effect, nor had it in three other cases in which it was subsequently used.

During June antistreptococcic serum was used, 5 c.c. being given every two or three days at first, and later 10 c.c., in all 125 c.c. being given. During this time the temperature varied from 99$\frac{1}{5}$ to 100$\frac{3}{5}$. Some time after beginning the use of the serum after each injection a free secretion of saliva occurred that was sometimes blood-stained. No apparent benefit followed the use of the serum.

He spent the summer of 1900 under most favorable conditions, living outdoors all day and sleeping in a tent at night. During the remissions the appetite was good and his diet highly nutritious. By September he was considerably better, but still his blood only

[1] Berliner klinische Wochenschrift, 1901, No. 17; abstracted in American Medicine, vol. i., No. 9.

contained about 3,500,000 red corpuscles per c.mm. In October on my advice he tried spermin (Poehl), 10 c.c. being given in divided doses extending over ten days. He soon began to improve, and during November his blood contained 4,500,000 corpuscles per c.mm., and the hemoglobin rose to 85 (Fleischl). He looked quite well and said he felt as well as ever. His corpuscles, however, showed considerable inequality in size, and a few nucleated ones could be found. He resumed his practice in a quiet way, but soon found himself unequal to the work. He became depressed; his mental condition, which had been affected early in his illness and was not completely restored even at his periods of greatest improvement, now became so much disturbed that he became difficult to nurse.

He was confined to bed, although the blood showed only moderate deterioration, and in January, 1901, he grew suddenly worse, and died comatose.

In more recent cases I have advised moderate purgation, with the object of removing infective material from the bowels. At the same time intestinal antiseptics have been given, and such general remedies as strychnine, arsenic, iron, bone-marrow, etc. The results, however, have been no less disappointing than former experiences.

Notwithstanding all the good work that has been done, the cause and pathology of the disease are as yet quite unknown, and as to its effective treatment we are equally in the dark. No plan of management or treatment so far devised avails to cure the disease or even, in most cases at least, alter its erratic course.

Before the recovery can be considered complete the blood, on histologic examination, must be found quite normal. A restoration of even the full complement of 5,000,000 red corpuscles per c.mm. is not sufficient, as that may occur in a prolonged and marked remission. Not a few of the cures reported have doubtless been remissions of this kind.

A CASE OF SO-CALLED SPONDYLOSIS RHIZOMELIA (RHEUMATOID ARTHRITIS), WITH AUTOPSY.

By CHARLES L. DANA, M.D.,
OF NEW YORK CITY.

SUMMARY. Male, aged thirty-five years; occupation, carpenter; moderately alcoholic; no rheumatic history. Brief attack of caisson disease, with paraplegia, seven years before. Present disease running a course of about one year; onset gradual, with pain in knees and hips; finally, extraordinary spastic condition of muscles of thighs, less so of legs. Death sudden. Postmortem showed no lesion of the spinal cord, but degenerative changes of the lining of the hip-joints.

The disease affected first and most strikingly the hip-joints, and for that reason may be classed among those forms of "spondylosis rhizomelia" which are nothing more nor less than rheumatoid arthritis. The case is particularly interesting because of the very extraordinary reflex symptoms which it presented, the obscurity of the symptoms at the onset, and the fact that a postmortem was obtained which enabled us to confirm absolutely the diagnosis.

History. The patient, J. R., male, aged thirty-five years, unmarried, native of the United States, was by occupation a carpenter. His father was a moderate drinker, and died of grippe at the age of forty-eight. Nothing is known of the family history aside from this.

The patient himself had the diseases of childhood, but denies any venereal disease whatever. He had been a steady drinker, and smoked and chewed tobacco; he used to get drunk once a month. Through an accident two years before he had two ribs broken, and the right wrist was broken one year ago. Seven years ago, while working in a tunnel, under high atmospheric pressure, he was suddenly taken with an attack of paraplegia. He was removed to a hospital; he was unable to control the urine at first, but speedily recovered power in the bladder and legs, and was discharged cured in three weeks.

About six months ago, while feeling very well he was taken with severe pain in the left knee, so intense that he had to stop work and go to a hospital in Havana, Cuba, where he was at the time. He remained in the hospital for three months, when he was brought to Bellevue Hospital on November 27, 1899 The pain which he first felt while in Havana was in the left knee. It was

constant, dull, and with exacerbations. From the knee it went to the hip, then to the right knee and hip. About two months after the pains began he noticed that his legs commenced to draw up so that he could not straighten them out, the hips and knees being both flexed. He walked every day a little, but it was very painful, and he had shooting pains at night, and his legs would jerk up in cramps. There never was any acute swelling of the joints or signs of any active process. His bowels had been regular, appetite good, mind clear. There was no weakness of the bladder.

The patient, on admission, presented the appearance of a very well-nourished man, weighing 178 pounds. He walked in a stiff, bent attitude, as shown in Fig. 1. He was unable to straighten the hips, and could not entirely straighten the knee.

Physical examination, outside of the nervous system, showed temperature, pulse, and respiration normal. Heart normal. Pulse somewhat hard, showing some arteriosclerosis. Tongue and digestive tract apparently normal. Urine 1010; no albumin or sugar. The blood was examined for plasmodium, and a blood-count was made, but the results were negative. The sleep was disturbed on account of the pain.

The muscular system showed very powerful development, especially in the lower limbs, the thigh muscles being extremely hard and much hypertrophied. There was a fibrillary tremor visible over the anterior thigh muscles which felt extremely tense, as if in a state of tonic contraction. There was no tremor excepting that found over the body of the muscles. The hands and face were steady. The patient could walk but little, as stated. The thighs could be flexed to the limit but could be extended only to about 135°. The left leg could be fully extended voluntarily, the right to about 15° from normal. The thighs could not be rotated in or out, and could not be adducted. In fact, flexion of the thighs was the only free movement, other movements being resisted by spasms of the antagonistic muscles. Thus, when the right leg was extended to about 75° the hamstring muscles were very tense, and when either thigh was extended to 135° the tendons of the quadrati stood out. The muscles felt like those of a man who has been trained to powerful muscular exercises. Whatever muscles could be moved passively could also be moved voluntarily. There was no distinct paralysis. The movements of the foot and ankle were normal, as were also those of the upper extremity. There was a slight compensatory lordosis, and the spinal column was somewhat rigid in its lower part.

The patient was thoroughly anesthetized, but with great difficulty, taking, I am informed, nearly two quarts of ether before becoming entirely relaxed. Then it was possible to extend the thighs and legs, but even then the motion was not very free, and when the patient returned to consciousness there was a gradual return of the contractions.

All attempts to move the hips and legs were quite painful except when the movements were in simple flexion. There was no enlargement of the joints, and no crepitation could be felt in either hips or knees. The reflexes were

decidedly exaggerated, and there was a distinct spurious clonus of the right leg. The superficial reflexes were exaggerated, but there was no Babinsky phenomenon.

The pupils were normal, the other special senses and cranial nerves were normal. There were no anesthesias and no ataxia, and no evidences of central nervous disease.

The specially remarkable characteristic of the case was the extraordinary tonicity and spasm of the thigh muscles unaccompanied by any evidence of inflammation of the joint, such as tenderness, swelling or fine crackling, or crepitations. The patient presented, in a measure, the symptoms that go with a case of spastic paralysis, and the exaggerated reflexes and ankle clonus led one to suspect a possible central lesion.

The condition continued without very much change for a number of months. The patient was anesthetized without any benefit. He received counter-irritation, warm baths, and antirheumatic measures. While his general nutrition did not become impaired, the disease continued about the same, there being at times some improvement, due to the use of hot baths.

In January, 1901, he suddenly died in an attack which was apparently one of heart failure.

The autopsy was made by Dr. Schultz, and the microscopic examination by Dr. M. G. Schlapp, to both of whom I am much indebted.

Dr. Schultz's Report. The heart weighs fourteen ounces; muscle paler than normal; few ecchymoses under the endocardium of the left ventricle, especially about the papillary muscle; the left ventricle, cavum, and wall of normal size; valves normal; right ventricle dilated, reaching to apex, which is markedly rounded; muscle at conus pulmonalis 3 mm. in thickness; columnæ carneæ well marked; width of wall toward apex 3 mm.; valves normal; blood, fluid and dark.

Aorta, normal.

Arteria pulmonalis contains dark fluid blood; a small postmortem clot is found in the superior branch in the substance of left upper lobe, not adherent to wall of artery. All other branches contain dark fluid blood.

Lungs: Left, passive hyperemia; right, old area of tuberculosis, bronchopneumonia at periphery of outer aspect of upper lobe, 3 cm. in diameter; pleuritic adhesions at this spot; passive hyperemia.

Stomach and intestines normal.

Liver, passive hyperemia; weight, five pounds twelve ounces.

Spleen, passive hyperemia; weight, twelve ounces.

Kidneys, passive hyperemia; weight together, seventeen ounces.

Adrenals, normal.

Pancreas, soft and slightly decomposed.

Bladder, normal.

Left hip-joint: Arthritis deformans; cartilage of head of femur and that of acetabulum markedly eroded. Synovial membrane thickened and granular; fluid diminished, light red in color; no pus.

Left knee-joint: Cartilage normal except a narrow strip (5 mm.) along the inner margin of femur; synovial membrane thickened and congested; crucial ligaments shortened, since flexion cannot be completed after tendons of patella and capsule have been severed.

Brain and spinal cord removed together. Dura and pia normal. Lumbar enlargement seems markedly smaller than normal. Further examination after hardening.

The only apparent abnormal condition of the cord was entire absence of lumbar enlargement. Meninges were normal.

No pathologic conditions were found in the cord or medulla on microscopic examination.

ACUTE SPLENIC MILIARY TUBERCULOSIS.

By D. D. STEWART, M.D.,
OF PHILADELPHIA.

THAT the tubercular process, whether in an acute miliary or more chronic form, may have its only outward expression in the spleen, and remain there entirely limited for a greater or less period, is a fact little recognized, yet one which has been emphasized by several recorded cases.

As a chronic affection, presumed primary tubercular splenomegaly is less infrequent than the acute miliary form. Bender,[1] who has recently published an exhaustive paper on the subject of tuberculosis of the spleen, alludes to some seven cases which he regards as instances of the former. In these Bender thought that the tubercular affection of the spleen was in so far limited to this viscus that involvement of other organs or parts gave no clinical manifestation. This, however, is an error concerning at least one of the cases which Bender quotes, in which splenectomy was performed—that of Bland Sutton. In this case Bland Sutton informs me the primary lesion was in the lung, and was of the nature of a "quiescent tuberculous cavity."

In Marriott's case[2] Bender is cognizant that the source of infection was perhaps a chronic vulvar ulcer which had been excised. Marriott had curiously reported this case as one of *acute* tuberculosis of the spleen. It is said there was no clinical indication of tuberculosis elsewhere, even at the end of two years, when a splenectomy was done, and eight months subsequently the patient was in good health.

It is not the purpose of this paper to discuss chronic tuberculous splenomegaly, but to draw especial attention to an acute form of miliary splenic tuberculosis, the occurrence of which, though ex-

[1] Gazette des Hôpitaux, March 31 and April 7, 1900.
[2] Lancet, November 23, 1895.

tremely rare, seems undeniable, and which, because of its rarity, has been doubtless occasionally overlooked. But a solitary case has been recorded—Scharold's[1]—and is most interesting. It is that of a convict who, apparently previously in good health and employed in out-of-door labor, was suddenly seized with symptoms suggesting an acute overwhelming general infection. There were high fever, prostration of strength, headache, cough, epistaxis, and diarrhea, retention of urine, delirium, and general cyanosis. The spleen was greatly enlarged. Death occurred on the seventeenth day. A necropsy showed a miliary tuberculosis limited to the much enlarged spleen. In the writer's case, although he cannot demonstrate that the infectious process was in onset or in early course limited to the spleen, yet he believes it is fair to assume this in view of the interesting symptomatology, and because the instance of Scharold's shows that such a limited miliary tuberculous process may occur and actually run its course without other involvement.

The writer's case was one in which more than ordinary interest was taken, both on account of its unique character and because of an acquaintanceship with certain of the patient's relations, one of whom, a physician, under whose observation she had previously been, watched the progress of the ailment with him.

The patient was Emma W., aged twenty-nine years; by occupation a nurse; single; of German parentage and American birth; the fifth of ten children, all living save one killed in a railroad accident. Brothers and sisters in good health. Parents living; father a dyspeptic, but otherwise well; mother in robust health. The family history otherwise offered nothing noteworthy; no tubercular antecedents.

Previous History. She had had as a child scarlet fever, measles, and pneumonia; had had ague seventeen years before, but had no indications of this since. She was of slender build, but quite robust, and had had no illness to incapacitate her for years. About four weeks before admission to the hospital, after just having left a trying and long-continued case of typhoid fever, she had had a slight grippal attack, lasting a few days. She was not confined to bed. Dr. Pottberg, her relative, had seen and prescribed for her. One week later, three weeks before admission to the Episcopal Hospital, when not recuperated from the grippe, ill-judged notions of humanity prompted her to take charge of a case of tuberculosis. The patient, living in her vicinity, had just lost his nurse; he was very ill and required constant attention. The consumptive, in indigent circumstances, had apartments which were

[1] Aerztliches Intelligenz-Blatt, August 7, 1883, No. 32.

badly heated and damp, and the nurse's nourishment was of poor quality. She ate irregularly, poorly, and lost sleep. She continued in charge for two weeks. In the middle of the second week she herself became rather acutely ill and had chills, with a rise in temperature, was debilitated and had pain and aching in the dorsal region. She still continued in attendance for a few days despite these symptoms, until a successor could be procured, and then went to her lodgings. There she remained about a week, abed, during which time the fever and debility continued. It is stated the temperature then ran between 101° and 103°, and she was presumed by her medical attendant to be developing typhoid fever. She was placed under my care at the Episcopal Hospital on about the tenth day of illness (April 18, 1900), and died the sixty-eighth day, fifty-eight days after admission.

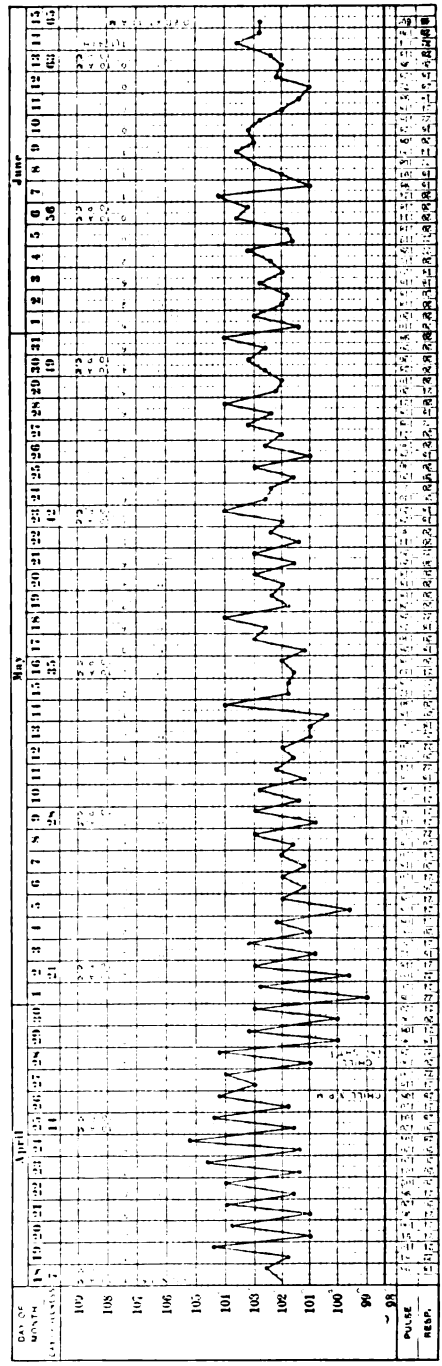
An examination on admission elicited: Mind active, though expression dull, with tendency to somnolence; but neither the dull expression nor somnolent tendency was manifest after a few days spent in the hospital. Had had slight chill every day or so since the ailment began.

Abdomen. No pain or tenderness or distention of the bowels. Spleen markedly enlarged, reaching above to sixth interspace, and inferiorly is readily palpable below the costal margin. No typhoid spots. Liver outline normal.

Chest. Heart sounds clear, though enfeebled; no murmurs. A searching examination of the lungs showed total absence of any indication of disease here. This repeated carefully daily gave similarly negative results until late in the progress of the case. The tongue was clean and of healthy appearance. This continued a feature until late in the disease. There was total loss of appetite, constipation, no nose-bleed. Temperature on afternoon of admission, 102.6°; on the following day it was 101.4° in the morning, and 104.4° in the evening. It was subsequently taken every third hour.

The accompanying chart shows the variations, and that the fever was a continuous one, with morning remissions and evening exacerbations. The average range was between 101° and 104°. The temperature only once reached 99° (in the morning), and but on one occasion (in the evening) 105.2°. The pulse was usually accelerated. The lowest noted was 84 and the highest 140. It showed wide and irregular variations. The number of respirations per minute were commonly in direct ratio to the body temperature.

Widal reaction and examination for plasmodia (Ghriskey) negative. (These examinations were made subsequently on alternate days for two weeks, with similar negative results.) Leukocyte count on admission, 5600. Urine, faint albumin trace; microscopically (centrifuged specimen) but one hyaline cast noted; otherwise negative. In arriving at a diagnosis the following ailments were considered: Typhoid fever, estivo-autumnal malarial fever, and acute miliary tuberculosis. The last was almost immediately suspected and within a few days decided upon, but solely by exclusion, as the general features of the case were unlike those of other cases of acute miliary tuber-


April
May
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DAY OF MONTH
PULSE
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culosis I had encountered. Here there certainly was as yet no lung involvement and no signs of abdominal implication other than the presence of the enlarged palpable spleen. The marked splenic enlargement indeed was the only notable physical sign other than the persistently high temperature and debility. There were for many days no other noteworthy clinical symptoms apart from occasional abdominal pain referable to the splenic region, and a tendency to cyanosis and continued blueness of the extremities when cold sponging was resorted to to reduce temperature. The patient's mind was clear and active, and she constantly reproached us for not ridding her of the fever, which she regarded as the only symptom of illness, that she might return to her home. Without other developments, the patient's condition underwent little change for the greater part of the fifty-eight days. The lungs were carefully ausculted daily, with negative results until about two weeks before death.

On May 14th two small glands were palpable in the left supraclavicular fossa. This was the first evident indication of dissemination of the tuberculous process. An ophthalmoscopic examination on this date (Dr. Van Pelt): Congestion of retinæ of moderate degree limited to each nasal side above the disc, more marked in O. S.

Toward the end of May marked debility was present as a natural result of the continued fever. She took but little nourishment, although free from gastrointestinal symptoms. At this time fine râles were evident now and then in both lungs. These, with vesiculobronchial breathing, were first noted posteriorly, her continued dorsal decubitus favoring stasis in the posterior surfaces of the lungs. On June 1st she had several spells of nausea and vomiting, and pain was complained of in the abdomen. Vomiting now recurred almost daily until death. She became delirious at night and had headache by day. It was noted on June 5th that the general body surface was markedly hyperesthetic; jerking and twitching of the limbs had occurred the evening before, and she frequently now gave a sharp outcry. She had been slightly deaf for several days, and was now markedly so. On June 12th the bedside notes record: "Deafness less apparent; responds more readily when questioned, though commonly delirious. Apparently is free from unprovoked pain, but remonstrates when the abdomen is palpated. Frequent twitchings of upper extremities, and these movements are accompanied by a harsh cephalic cry. Kernig's sign is absent. Tache cerebrale marked. Abdomen much distended. Tongue for first time dry and brown in color, sordes appearing. Pulse intermittent. Yesterday a bright red circular area, about one inch in diameter, appeared on the back of the left hand. It had a distinct white border and was covered with vesicles. The whole hand was swollen and somewhat red. To-day the vesicles have united into one very large one, and similar spots have appeared on the thumb and fingers. Cultures from the vesicles show staphylococci." On June 15th the notes state: "The patient was rigid for the past two days. Kernig's sign still absent. Drooping of right eyelid noted. Emaciation now becoming extreme. Area on hand

has formed superficial slough. The patient's outcry is less shrill, and jerking of the limbs is less marked. She is more or less comatose, constantly moans, and no longer responds rationally to questions. Marked weakness is apparent. Pulse continues intermittent. The patient died cyanosed on the morning of June 15th."

Clinical pathologist's (Dr. Ghriskey) report: No indications of kidney involvement until late in the case. Albumin and casts absent in the early period of the disease. Numerous blood inspections negative, save for a leukocytosis first noted June 12th. Several examinations of the erythrocytes were made, the last May 10th—3,800,000. Hemoglobin estimated on several occasions early in the disease, 65 to 75 per cent. Leukocytes frequently estimated; counts ran between 5000 and 6000 until on June 12th, 14,800 (terminal infection). Malarial parasites: Frequently examined for early in the case, and always negatively. During the first week the blood was also drawn from the spleen for this estimation. Unfortunately, tubercle bacilli were not examined for in this specimen. Cultures from this (for typhoid) were made; result negative. In the middle period of the disease 4 c.c. of blood from a vein was diluted, centrifuged, and examined for tubercle bacilli; result negative. Several sputum examinations were made the last of May and early in June, and no tubercle bacilli found. Diazo reaction examination on several occasions was negative at first, but positive on May 7th. Cultures from vesicles on hand and from meninges of brain showed staphylococci. Other cultures at postmortem negative. Microscopic: Typical miliary tubercles in kidney, liver, and spleen.

Report of the necropsy and gross and microscopic examination of specimens by the Episcopal Hospital Pathologist, Dr. W. E. Robertson, June 15, 1900: The body is that of a slender young woman. Rigor mortis absent. A large bulla noted on dorsum of left hand.

Thoracic Cavity. Lungs and heart taken out together. Heart presented nothing abnormal. Lungs: The seat of diffused, very small miliary tubercles. No consolidation. Lungs crepitated throughout. Moderate pleural adhesions on both sides. Several medium sized lymph glands in left supraclavicular fossa, enlarged and caseated, and resting upon subclavian artery.

Abdomen. Slight amount of fluid and some injection of intestines. No tubercles on mesentery or peritoneum; intestines and stomach were examined throughout. No typhoidal or tubercular lesions. A few shallow ulcers or erosions on the membrane of ascending colon. Liver slightly fatty, but firm, and presented fairly numerous minute tubercles through it. No gallstones. Duct patulous. Kidney capsules stripped with ease; section showed cloudy swelling; apparent slight interstitial change. Few small miliary tubercles evident near capsule.

The most noteworthy feature of the examination was the spleen. This was about four times the normal size. It was studded on its peritoneal coat with elevated yellow tubercles the size of a large pea and surrounded by an inflammatory zone. "On section the whole organ was found to be a mass of

tubercles, varying in size from a pin-point to four mm. in diameter; these, to about the extent of one-half the spleen, had advanced to complete caseation, converting this part of the gland into a confluent tubercular mass, in which, while the outline of some of the tubercles were still apparent, in the greater part there was merely evident a most marked cheesy necrosis. Such a condition was found nowhere outside the spleen."

Pancreas normal. Bladder distended; wall thick-looking and vessels in it turgescent. Urine blood-tinged. Wide-spread submucous extravasation of blood; the blood could be neither wiped nor washed off. There was nothing to explain this high grade of hyperemia, which resembled that met with in some cases of paraplegia, or in cases in which the circulation through the inferior cava is interfered with. Such a condition is sometimes seen in hemorrhagic diseases, such as scurvy, and it is possible that in this case the intensity of the infection may have induced it, as it did the blood extravasations in the kidney and spleen.

Brain. The dura bulged on removing the skull-cap. A large amount of fluid escaped when it was cut. It was quite adherent over the region of the Pacchionian bodies. In this region, too, a slight amount of puriform material was found, and also in a few other places scattered irregularly over the cortex, these latter in the subarachnoid space apparently. Adhesions in fissures at base. Miliary tubercles along the small vessels in the fissure of Sylvius. Cord not removed.

Histologic examination of liver, kidneys, and spleen:

Liver. Parenchymatous degeneration. Slight increase of perilobular connective tissue and a tendency to multiplication of the bile capillaries. Numerous microscopic miliary tubercles, the large majority being in an early stage, only an occasional one presenting some cheesy necrosis. There was no confluence of tubercles.

Kidney. Slight diffuse parenchymatous degeneration. Numerous microscopic miliary tubercles, for the most part early, though there were a few which were decidedly degenerated in their centers, and here and there some coalescence had taken place, so that the mass was visible to the naked eye, though very small.

Spleen. Presented the most pronounced tuberculous condition far more than any other organ in the body. In addition to countless miliary tubercles in a comparatively early stage—these being far more numerous than found in the other organs—were confluent tubercles, many of them small others very large, and all in an advanced stage of necrosis, about one-half of the organ being appropriated by this conglomerate tubercle mass. Both kidneys and spleen were much congested, and extravasations of blood were common, especially in the spleen.

There is an interesting similarity between the case of the writer and that of Scharold before mentioned. Like Scharold's, my patient became acutely ill, but having greater resisting power, the manifesta-

tions of general infection were much less overwhelming and the duration of the illness considerably more extended. Scharold's case died on the seventeenth day; mine on the sixty-eighth. Like Scharold's, enlargement of the spleen was noticeable early. This, with other acute manifestations, had naturally caused the attendant prior to admission to the hospital to regard the case as one of early typhoid fever, and she was received with this diagnosis. Unlike Scharold's case,[1] symptoms and physical signs suggestive of pulmonary involvement were totally absent, and their continued absence, with a similar dearth of localization of the tuberculous process elsewhere, was regarded as most singular. As detailed in the history, other than the splenic enlargement and continuous and rather high temperature, there was a curious absence of symptoms through the greater part of the course of the case. The splenic enlargement reached its maximum rather early and showed no increase after the third week of illness. The spleen was not notably sensitive to pressure until late in the disease. Unlike Scharold's (Scharold gives only the macroscopic appearances of the presumed uninvolved organs) case, the tubercular process had generalized when death occurred. Miliary tubercles were then evident in the brain, lungs, liver, and kidneys. Those in the lungs, though disseminated, were recent and minute, the lungs showing no indications of consolidation. But few also were manifest macroscopically in the liver and kidneys, and none existed in the peritoneum or in the gastrointestinal tract, uterine appendages, or bladder. The process was so extensive and advanced in the spleen, and so extraordinarily out of proportion to that encountered elsewhere, that Dr. Robertson, though unaware of the history, at once remarked the case was evidently one of primary miliary tuberculosis of this organ; and this, I believe, we must so regard it.

Infection in this case apparently arose through the consumptive the patient was nursing. It must, of course, have occurred early in her contact with him, as symptoms appeared acutely about the middle of the second week. She had gone to the case for humanitarian reasons, and contrary to the advice of her friends, a week after the onset of a mild attack of supposed grippe. Though this had not confined her to

[1] I was then unaware of the case of Scharold. My attention was drawn to it subsequently by Dr. W. E. Robertson.

the house, she stated she still felt weak. Immediately prior to this she had left a convalescent typhoid patient, in which case she had been the sole nurse, and had continued with it for two months. She was now ill prepared to undertake the arduous duties which devolved upon her in nursing the consumptive. As before remarked, this patient's rooms were damp and cold, the nurse was constantly in attendance, lost much sleep, and was poorly fed.

A CASE OF ACUTE LEUKEMIA PRESENTING SOME INTERESTING FEATURES.

By D. D. STEWART, M.D.,
OF PHILADELPHIA.

THE accompanying case might not be deemed worthy of report, because of the incompleteness of the record, were there not very special features of interest that demand its publication. The patient was in the writer's wards of the Episcopal Hospital, in the spring of 1899, for thirty days prior to her death.

She was admitted with symptoms which several inspections of the blood, showing evident leukopenia, caused the diagnosis of scurvy to be made. These were: Spongy, hemorrhagic gums, with looseness of the teeth, fetid breath and furred tongue, an anemic appearance, and a tendency to nose-bleed. The patient had been debilitated since the birth of her last child, three months before, and the above symptoms had since developed. Appropriate treatment for scorbutus was ordered, and but little further attention was paid to the case until she was well into what appeared to be an attack of typhoid fever. The history is as follows:

Ann S., aged twenty-eight years; birthplace, Philadelphia; occupation, housework. Admitted to the Episcopal Hospital April 11, 1899. Death, May 11, 1899.

Family History. Father said to have died of heart disease; mother of insanity. Otherwise family history negative.

Previous History. Had measles when a child; no other infectious disease. Fairly healthy until lately, save that she had had a bad diarrhea after the birth of one of her children. No specific history; never had had chills and fever. Married for nine years; five children; last child born three months before admission. Had nursed child for one month. She was of slender build, and her complexion was said to have been always pallid.

Present Illness. Began some two or three months before (about February, 1899), shortly after the birth of her child; then the gums became swollen and

bled easily. There has since been a tendency to nose-bleed, but no hemorrhage from other parts of the body. On admission it was noted that the patient presented a rather anemic and markedly ill-nourished appearance, which she said was habitual with her. There was a history of overwork and privation. The gums were much swollen, soft, and spongy, almost covering the teeth in places, and tended to bleed easily. There had been no salivation, and she had not taken calomel. The teeth were quite loose and the breath very foul; the tongue swollen and furred. The heart sounds were enfeebled; no murmurs were present. Indications of enlargement of the external lymph glands were not evident, and the area of splenic dulness was little increased over the normal.

An inspection of the blood by Dr. Ghriskey on several occasions during the first week of admission invariably showed a diminished number of leukocytes, a number of fields having to be covered for one to be seen. Red corpuscles pale, not distorted. No estimation of red or white corpuscles was then made.

An astringent mouth-wash was prescribed. She was given a nourishing diet, containing such green vegetables as could be procured, and expressed meat juice and lemonade. Tincture of iron in syrup of lemon was prescribed, and a moderate amount of strychnine and whiskey ordered. Her temperature from the day of her admission is as recorded on the accompanying chart.

On the day of her admission (April 11th) and that following it varied from 100° to 101°, reaching 103.1° on the 13th, but subsequently, until the 19th, it did not exceed 100°. It had then begun to show a gradual rise, suggestive of typhoid fever.

There was a great deal of typhoid fever in the wards at the time, and, coincident with the occurrence of the more or less characteristic temperature rise, it was suspected she was developing this disease. During the latter part of April her spleen, which on admission had not been palpable, was now notably so. There was diarrhea, and spots had appeared on the abdomen which superficially resembled the rash of enteric fever, and on May 2d the blood was reported to give a typical Widal reaction. The examination was made at the City Laboratory by Dr. A. H. Stewart, from a dried specimen. Unfortunately, a second specimen was not sent. The abdomen had become distended, and there was marked tenderness in the right iliac region.

On May 7, 1899, it was noted that the rash had become general, and was unlike that of typhoid fever. The spots had much increased in size, and in places were becoming purpuric. Much aching was complained of in the extremities. The breath was highly offensive; the gums hemorrhagic and sloughing at several points. The heart sounds were much enfeebled; the spleen had become much enlarged, and was palpable two finger-breadths below the costal margin. The bowels were now very loose. An inspection of the blood, which had not been made since the first week of admission, showed an extensive leukocytosis, the large mononuclear cells prevailing.

The report was: Leukocytes, 89,600; erythrocytes, 1,280,000; hemoglobin, 25 per cent. Urine (catheterized specimen) turbid; contains numerous whitish flakes in suspension; reaction acid. Albumin, marked trace to heat and acid. Microscopically, numerous leukocytes, singly and in clumps; granular and epithelial casts; many erythrocytes.

On May 9th it was noted that the purpuric rash had become more or less general and tended to be confluent. Leukocyte estimation 102,000.

May 11, 1899. Leukocyte estimation made, but report missing. It is recalled that the count was considerably in excess of that of the 9th inst. She had a moderate hemorrhage from the bowel on the evening of the 10th, and a very large one the following morning. This was followed by symptoms of collapse. Despite repeated hypodermoclysis and other measures to restore her, she died the evening of the 11th. In the last week of her illness diarrhea was excessive.

Pathologic Report by Dr. Robertson.

"Necropsy made six hours after death. Body of a rather emaciated woman. Purpuric spots over abdomen; gums soft and swollen, and overlapped teeth more than normally; subcutaneous fat greatly diminished; musculature very poor.

"*Thorax.* Pericardial fluid normal in appearance and amount. Heart muscles pale and flabby; valves and orifices normal; weight 256 grams. Hemorrhagic foci on visceral layer of the pericardium. Lungs: Calcareous nodule in apex of right lung; otherwise both are normal throughout.

"*Abdomen.* Stomach low in position. Kidneys, both movable, the right one freely, the lower margin being on a level with the crest of the ilium, though some attachment still remained, being formed by the original perirenal tissue, which had been converted into a long band. Both kidneys pale on section; cortex widened, due to parenchymatous degeneration. Right kidney weighed 208 grams, the left one 256 grams. Liver enlarged, rather pale, seat of parenchymatous degeneration. Spleen much larger than normal; weight 432 grams. Quite firm; unlike that which one finds usually in typhoid infection. Intestines: Small bowel contained no ulcers. Peyer's patches distinctly visible, owing to numerous small pigmented spots within them. There were no signs of inflammation anywhere. The cecum, ascending and transverse colon contained many deep, ragged ulcers, many with black hemorrhagic sloughs partly separated. A few of the ulcers were perilously near perforation, the serosa alone remaining, and this latter on its peritoneal surface and the juxtaposing peritoneum was congested and roughened. Large blood-clots were found in the large bowel. These ulcers did not resemble any typhoid ulcerations that I have ever seen. They were very irregular in outline, and the erosion itself seemed to have progressed with varying degree of rapidity in the same ulcer, hence the bosselated character, the unevenness of the base. The appendix, which was very long, contained two small ulcers near its tip. Unfortunately, no special study of the bone-marrow was made, the ribs and

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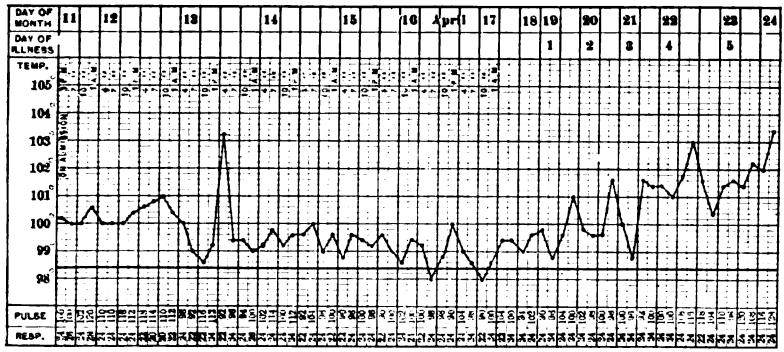
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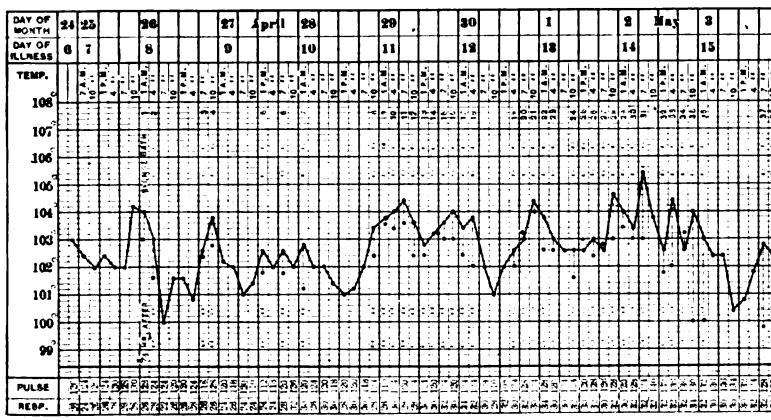
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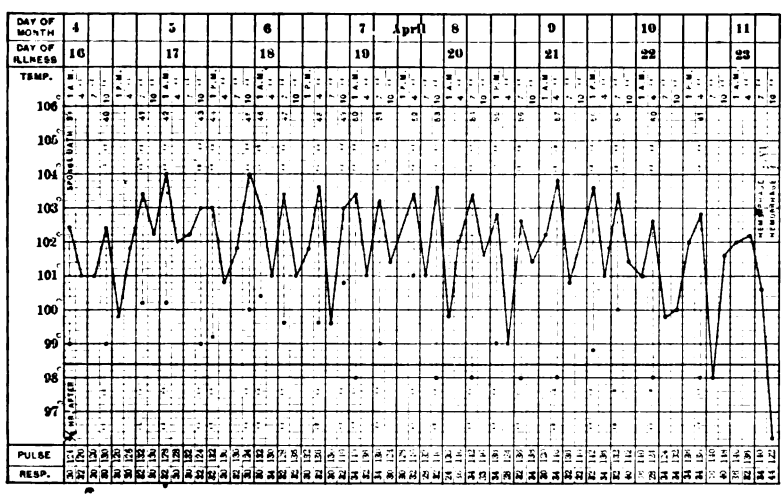

DAY OF MONTH
DAY OF ILLNESS
TEMP.
PULSE
RESP.
April

sternum alone being examined, and here it was normally of the red variety. The inguinal, mesenteric, and peribronchial lymph glands were enlarged and firm.

"Microscopically the ulcerated portion of the intestine appeared as follows: The mucosa was completely necrotic, and sections stained with thionin showed numerous micro-organisms, chiefly bacilli and streptococci. These had not penetrated very deeply into the submucosa. The lymphoid tissue had been infiltrated with plasma cells and large and small lymphocytes, so that as a matter of fact the normal adenoid tissue had been obliterated. Numerous plasma cells and mast cells were found scattered throughout the submucosa.

"*Spleen.* Vessels thickened; Malpighian corpuscles much less marked than normally, being apparently largely displaced by the very rich cellular parenchyma. Plasma cells and large endothelial cells seem to make up the large part of these. No bacteria could be found.

"*Lymph Gland.* The normal arrangement of a lymph gland is totally lost. It is very rich in cells, plasma and endothelial, the latter apparently descendants of the cells lining the lymph vessels and spaces. Small and large lymphoid cells, aggregated into groups and surrounded by attenuated fibrous tissue, on an approach to the normal, was only found in the periphery of the gland. No micro-organisms found.

"*Liver.* Parenchyma cells swollen and granular, the seat of parenchymatous degeneration. No increase of connective tissue or bile-ducts, but here and there aggregations of lymphocytes and connective-tissue cells.

"*Kidney.* Seat of parenchymatous degeneration; moderate congestion. About the glomeruli and between some of the tubules, particularly in the neighborhood of the glomeruli, were aggregations of plasma cells and large lymphocytes.

"*Heart.* An interstitial collection of plasma and connective-tissue cells and a few lymphocytes. Muscle fibers stain well.

"From the histologic examination the picture is that of any of the acute infections plus the great increase of lymphocytes. The plasma cell has been found particularly in typhoid and diphtheria, but is met with in other infections also, though I scarcely think in as great numbers. How large a part they play in scurvy or acute leukemia I do not know."

Specimens for microscopic examination were also submitted to Prof. Simon Flexner. The following is his report:

"*Intestine.* The section of intestine consists of a nodule equally within the mucous membrane and the adjacent tunic, including a portion of the omentum. The nodule occupies the whole of the mucous membrane as far as contained within the section, with the exception of a fragment of tissue, at one end in which the crypts of Lieberkuehn are still present. With this latter exception the entire tissue is degenerated and refuses to take the

staining agents. The remainder of the membrane is made up by cells separated by a stroma, in some plases coarse in texture and in others fibrillar. The degenerated edge goes over quite sharply into the cellular layer, and there the line of demarcation is occupied by brightly staining cells and intercellular tissue.

"As regards the preserved portion of the cellular infiltration, it consists of cells of large size possessing vascular nuclei, the latter being reticulated, and an abundance of protoplasm. Among these are small cells resembling lymphoid cells in all particulars. Many of these cells show karyokinetic figures. These figures are especially marked in the larger cells described; they exist throughout the nodule, are about uniformly distributed, and in the preserved edge of the tissue, just below the degenerated tissue, are present as described. These dividing cells show all stages from the simple dividing aster to the completely divided nucleus; rarely four or five nuclei are found contained within a single cell. The infiltration described involves the mucous membrane and submucosa, so that no distinction can be made out in these two tunics. The muscular coat, on the other hand, is less uniformly affected, but in it are islands of cellular tissue, presenting the same characters as those of the mucosa and submucosa. The cells composing the nodules are made up chiefly of the larger cells described. Among these there is also evidence of karyokinesis. The peritoneal coat is very diffusely infiltrated with similar larger cells chiefly, although some of the smaller lymphoid cells are also present, and cell division is going on among these cells. The bloodvessels, chiefly of the muscular coat, show an increase of white elements, especially of larger white elements with single nuclei, and it is found that nodules in the muscular coat had developed about such bloodvessels, and perhaps also about lymphatics. The type of large cell agrees with the type of large mononuclear leukocyte as found in the blood, and they may be considered as being alike, inasmuch as those within the vessels agree with those without the vessels. That the nodules have arisen, at least in part, by proliferation *in situ* is shown by the active karyokinesis.

"*Mesenteric Gland.* Section of this gland shows that it is not greatly enlarged. Upon microscopic examination there is seen hyperplasia of the entire gland, which largely obliterates the distinction between the cortex and medulla, and in which there are numbers of cells having the general characteristics of large mononuclear leukocytes. In these cells karyokinesis is also apparent.

"*Spleen.* Shows a considerable amount of yellow blood pigment. It is uniformly infiltrated with cells; rarely can a Malpighian body be made out. The cells are of the type of lymphocytes, the larger ones chiefly being represented. Cellular accumulations are found, especially in the pulp. Karyokinesis also appears in the large cells.

"*Liver.* The cells are granular; the capillaries contain a greatly increased number of white elements which partake especially of the character of lymphocytes. In addition to which there are scattered nodules of cells

surrounding branches of the hepatic veins especially, consisting of large lymphocytes admixed with a small number of small lymphocytes. These occupy the sheath of vessels and extend into the liver tissue and take, in part, its place. Karyokinesis is also to be seen among these cells.

"*Kidney.* Shows swelling and granular degeneration, and some fatty degeneration of the tubular epithelium. It also shows small hemorrhages into the tubules and focal accumulations of the large mononuclear elements within the kidney substance, chiefly about the glomeruli.

"*Heart.* Section of heart muscle shows, first, an increase in fibrous tissue about the larger bloodvessels; second, focal accumulation of cells, chiefly of the type of lymphocytes between the muscle fibers. These accumulations are often elongated, adapting themselves to the space between the fibers. An occasional nucleus, such as are found in polymorphonuclears, and an occasional red cell are also found.

"*Diagnosis.* These sections come from an undoubted case of lymphatic leukemia of the large mononuclear type. The bloodvessels contain greatly increased numbers of these mononuclear elements. From the bloodvessels they have escaped into various situations of the body, especially into the intestinal mucosa and submucosa, where they have developed with the production of leukemic nodules."

A differential blood-count was made for me by Dr. Thayer, of the Johns Hopkins Hospital, for which I here express my great indebtedness. It is as follows:

"The specimen of blood which you sent me is very remarkable. It is clearly an example of large-celled lymphatic leukemia. I have seen similar bloods in two instances of very acute lymphatic leukemia—in one associated with hemorrhagic and extensive areas of cutaneous gangrene. The type of blood is that which in my experience is associated with the most rapid and malignant type of lymphatic leukemia. The two specimens were stained—one with Ehrlich's eosin-hematoxylin, the other with the triple stain. In the first place, the specimens stained badly. Whether with the triple stain or with other stains, the ground substance between the different cells takes a distinct color, a slight, diffuse lilac stain in specimens stained with the triple stain, and a more reddish color in the eosin-hematoxylin specimen. This is especially marked round about each leukocyte. The red corpuscles show moderate variation in size—a slight, though not great, poikilocytosis. No nucleated red blood-corpuscles were seen. There is a great increase in the number of leukocytes, which are almost entirely mononuclear. Many of these, however, show nicks and divisions in the nucleus, for the most part not like those occurring in the ordinary development of the polymorphonuclear leukocyte. The most striking feature about the specimen is the almost absolute lack of granules. Scarcely a single element containing undoubted neutrophilic granules has been found. After considerable search

a single eosinophile was seen. The mononuclear elements consist of typical small lymphocytes with deeply-staining nuclei, which nearly fill the cell body, and of elements larger than these all the way up to bodies larger than the ordinary polymorphonuclear cells. These, as has been said, show in many instances nicks which are sometimes deep, so as occasionally almost to divide the nucleus in half. On account of their general similarity in character to the larger mononuclear cells, these have all been classed as mononuclear elements. The protoplasm of some of these elements is deeply staining, of a brownish or slightly lilac color, of others with grayish, and of others nearly colorless. The number of cells with nuclei like those of the ordinary polymorphonuclear leukocyte was small. A differential count of a thousand leukocytes showed: Typical small lymphocytes, 16 per cent. Mononuclear elements smaller than the ordinary polymorphonuclear leukocyte, usually with palely staining nucleus, some showing nicks as above referred to, 22.4 per cent. Cells as large as polymorphonuclear leukocytes or larger, with a nucleus usually palely staining, 55.6 per cent. Cells with distinct polymorphous nucleus, and some showing a suggestion of granulation, but no positive neutrophilic granules, 6 per cent. No nucleated reds or eosinophiles were found among the thousand counted."

An analysis of this case has been puzzling to me. At the time of its observation my notion was that on admission to the hospital it was one of scurvy, that typhoid infection had then occurred, and that the acute leukemia had appeared as a complication of the presumed typhoid fever. The patient had been ailing for two or three months, and on admission her gums were spongy, much swollen, and hemorrhagic, and the teeth loose. Yet several inspections of the blood by Dr. Ghriskey, whose careful technique is well known, showed an evident leukopenia. It is well known that in ordinary spleno-medullary leukemia there may be periods in the course of the disease in which, with or without extensive splenic enlargement persisting, the leukocytes approach the normal in number, or even fall below, and that the separation of such a case from ordinary splenic anemia must be made by the persistence of myelocytes in considerable number. Ordinarily, lymphatic leukemia is acute in its onset and course. In the less common chronic cases there are, I believe, no observations showing the intercurrent existence of periods in which the leukocytes diminish to normal or fall below, and in which a high percentage of lymphocytes persists. With glandular enlargement evident such a case would be indistinguishable from Hodgkin's disease, in certain cases of which there may be increased percentage of lymphocytes

without the total number of leukocytes being above the normal. In the present case it is difficult to conceive lymphatic leukemia without leukocytosis and without evident external glandular enlargement, which in this case did not exist on admission, and only occurred toward the termination of the case; there then was moderate swelling of the cervical, axillary, and inguinal glands. In the present case I am forced to conceive a preleukemic blood state in which, without leukocytosis, if a differential count had been made on admission, a high percentage of lymphocytes would probably have been found to exist. But as a lymphocytosis may occur in scurvy, the diagnosis of possible leukemia would have been favored less by this than by the febrile temperature, and the lack of prompt improvement in the case under an antiscorbutic regimen. The woman was of the lower class; had for years overtaxed her strength, and had been ill-nourished. She had just passed through gestation and a month of lactation, so that the conditions were favorable for the development of any morbid blood state. Bearing in mind the aping of the clinical picture of typhoid fever by acute leukemia, it is still conceivable, though not altogether probable, that this patient had, preceding the development of undoubted acute leukemia, a typhoid infection. Certainly spots appeared which were regarded similar to those of typhoid,[1] and the blood was reported by Dr. A. H. Stewart, of the City Laboratory, who has had an extensive experience in such examinations, to give the typical Widal reaction.[2]

Unfortunately, cultures were not made in life or after death to determine the existence of the typhoid organism. The importance of such cultures was recognized; they were requested repeatedly, but in the very large amount of detailed labor then thrown on Dr. Ghriskey in the organization of the clinical laboratory, then in its incipiency, and who was working without an assistant, they were omitted.[3]

The postmortem picture was that of an acute severe infection.

[1] But the minute character of which no record exists, as the condition was then thought to be typhoid fever.

[2] The Widal reaction was examined for but once, and from a dried blood specimen. We had not then begun such examinations at the hospital.

[3] The hospital at this time was much overcrowded. Beside the usual run of cases there were, coincidently, seventy-eight cases of typhoid fever. This service naturally entailed both on myself and Dr. Ghriskey and the residents an excessive amount of routine work, and more than could be adequately well done.

The ulcers, the erosion of a vessel of one of which had caused the fatal hemorrhage, were limited to the colon. Dr. Thayer's report of the blood condition is especially interesting, in that it shows the case to belong to a type of very acute malignant leukemia. This argues against the existence of a disease nearly four months before, at the time of the appearance of spongy gums, and with the absence of a leukocytosis on admission to the hospital a month before. My own judgment is, viewing these and other facts in the case, that the leukemia was but in its incipiency on admission; that it had very acute onset, with the gradual rise in temperature suggestive of typhoid fever; that the earlier conditions represented a blood dyscrasia allied to scurvy, upon which the very acute and fatal leukemia was subsequently engrafted.

A CASE OF MALARIAL NEPHRITIS, WITH MASSING OF PARASITES IN THE KIDNEY.

By JAMES EWING, M.D.,
OF NEW YORK CITY.

The frequent occurrence of renal lesions in malarial fever was described long before the discovery of the malarial parasite, and has been very constantly recognized throughout the progress of our knowledge of the disease.

Owing to the studies of Rempicci, in Italy, and of Thayer, in America, it is unnecessary to again review in detail the contributions of the various observers in this important field. On the evidence collected and largely contributed by these two writers one may now state with confidence that albuminuria is nearly constantly present in pernicious estivo-autumnal infections, and is frequently observed in the milder tertian cases. Of greater interest and importance are the rather numerous records of distinct signs of an acute exudative process in the kidneys, usually in estivo-autumnal cases, less often in tertian infections, and consisting in the presence in the urine of epithelial and granular casts, many blood-cells, as well as considerable albumin. Although the milder changes in the urine may develop, according to Rempicci, either during or shortly after the acute attack, it would seem that the more severe urinary signs can be safely attributed to the malarial infection only when arising in the course of a pronounced acute seizure.

Recovery has usually followed the acute symptoms, but Kelsch and Kiener, Laveran, Marchiafava and Bignami, Rempicci, and Thayer have described various types of chronic nephritis occurring in long-established or chronic cases of malaria, while Kelsch and Kiener state that the chronic nephritis of malaria is distinguished from other types by the prominence of hemorrhages and the comparative absence of fatty and hyaline degeneration and of arterial changes.

The acute nephritis of malaria is almost never immediately fatal, so that the pathologist must speak with reserve regarding the origin and significance of many of the cases of exudative nephritis commonly attributed to malaria. In view of the frequent clinical reports of the presence of considerable albumin, many casts, and of blood-cells in the urine, and less often of edema and mild uremic signs in the disease, it seems certain that during severe malarial infection a true exudative nephritis is sometimes excited. Even in the absence of pathological examination of the kidneys these symptoms may with some confidence be referred to congestion of vessels, acute degeneration of cells, and exudation of serum and diapedesis of red cells from the bloodvessels, all dependent upon the action of the malarial toxin upon the renal tissue.

Coming now to the fatal cases of pernicious malaria in which there has been a microscopical examination of the kidney, the conditions found in this organ in all except hemoglobinuric cases have been very uniform. The lesions observed have been those of a severe acute degeneration of the cortical tubule cells, with moderate exudation of albumin into the tubules and glomeruli.

The chief contributions in this field have come from Guarnieri, Marchiafava and Bignami, Monti, Bastianelli, Barker, and Benevenuti. In all of the reports of these observers the nephritis has been clearly of toxic origin, while the number of parasites found in the kidney has been small, although they were usually very numerous in other tissues. The single exception to this rule is found in one of Barker's cases, in which death and probably the recent changes in the kidneys were principally referable to general infection by streptococcus pyogenes. Here the renal capillaries were frequently thrombosed by masses of streptococci and large numbers of tertian parasites. This case cannot, therefore, be regarded as one of malarial nephritis, but rather as an example of pyemia or septicemia terminating the usual benign course of a tertian malarial infection.

The invariable freedom of the kidney from localization of parasites in pernicious cases cannot be attributed to the phagocytic powers of this organ, which enjoys only a moderate capacity to destroy parasites. Guarnieri, who noted the small number of parasites in the kidneys of his and other cases, referred this comparative immunity to the rapid circulation of the organ.

The examination of the records of microscopical examinations of the kidneys in malarial fever fully warrants the latest conclusions of Marchiafava and Bignami regarding the origin of the renal changes in pernicious malaria, which are as follows, quoting from their article in the *Twentieth Century Practice:*

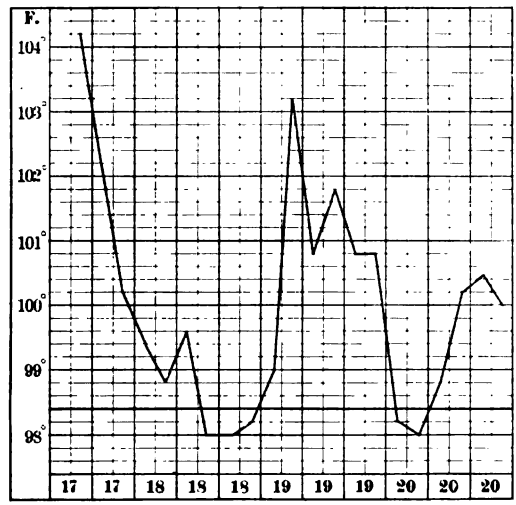
"As to the pathogenesis of the renal lesions in malarial infections, we are at present able only to form theories. The knowledge of the parasite has so far thrown no light on the pathogenesis of the nephritis. In pernicious infections very few parasites are found in the kidneys, even when the changes in the epithelium may be so grave as to lead to necrosis. From this fact we may infer that the lesions are due not to a localization of parasites in the renal capillaries, but to some toxic substance eliminated by the kidneys."

My own experience in the examination of fourteen fatal cases of malaria, seen mostly at Montauk, in 1898, fully accorded with the above conclusion, as I found, usually, extensive degenerative changes in the kidneys, once the lesions of hemoglobinuric malaria, but comparatively few or no parasites in the renal vessels. The present case, recently encountered, developing in the vicinity of New York, showing the clinical symptoms of acute hemorrhagic nephritis with partial suppression of urine, and giving clear microscopical evidence of extreme massing of parasites in the kidney, with various mechanical lesions resulting from their presence, seems to require a reversal of the above conclusion, and appears to show that malarial nephritis may be caused principally, or in large part, by the presence of an excessive number of parasites in the renal capillaries.

The patient was a friendless girl, aged seventeen years, a Slav, who had been in America one year. She had enjoyed good health until going as a servant to College Point, Long Island, in July, 1900. She was discharged early in September on account of an alleged "inability to work," and this fact, together with a distinct pallor and slight jaundice noted on her return to the city, indicates that she had suffered for some weeks from malaria contracted on Long Island. September 12th she was taken acutely ill with chills and fever, and being without the help of a physician, she became steadily worse until brought by ambulance to the hospital, on September 17th.

On admission, the patient was well nourished; tongue moist, slightly coated, prostration marked; physical examination of lungs, heart, and liver was negative; the area of splenic dulness was enlarged, but the organ was not palpable; there was slight edema of the legs; the urine, voided naturally in

moderate quantity, was described as of high color, clear, acid in reaction; specific gravity 1018; urea two and a half grains to the ounce; albumin 2 per cent. by volume; sugar absent. Microscopically there were noted epithelial cells, many red blood-cells and amorphous urates; diazo reaction marked; temperature 104.2°; pulse 98. On September 18th there was vomiting of food and medicines; constipation was relieved by enemas; retention of urine, with marked diminution in its quantity, which continued until death. Delirium developed on September 19th, and was controlled by morphin, sulphonal, and choralamid, given at intervals, on the 19th and 20th. On the 19th she vomited a round worm, and was given at intervals three doses of santonin, three, five, and fifteen grains, without any change being noted in the urine, stools, or conjunctiva. Delirium continued on the 20th, and the pulse failing steadily, she became comatose, and died at 9 P.M. The temperature-chart is appended. The clinical diagnosis was typhoid fever, with acute nephritis.



Autopsy by Dr. Otto Schultze, thirteen hours after death. Body well nourished; rigor well marked. Heart normal; an ounce of straw-colored fluid in pericardium; a few ecchymoses in visceral pericardium. Lungs: A few old pleural adhesions; a few ecchymoses in visceral pleura. Liver appeared normal. Pancreas normal. Stomach normal. Ileum congested, solitary follicles moderately swollen. Colon congested. Spleen much enlarged; weight sixteen ounces, consistence firm; Malpighian bodies prominent; pulp dark red. Kidneys together weigh sixteen ounces; consistence reduced; capsule free; cortex remarkably light in color. Medulla and papillæ extremely dark and slightly rust-colored; cortical markings entirely obscured. In the cortex of right kidney there is a superficial anemic infarct

with surrounding hemorrhagic zone. This infarct measures 3½ x 2 cm. in area, and 2 mm. in depth.

Anatomical Diagnosis. Acute hemorrhagic nephritis. There was still no suspicion of malarial infection. Cultures of liver, spleen, and kidney yielded bacillus coli and putrefactive species.

Through a misunderstanding all the viscera, except the kidneys, were thrown away. The kidneys were hardened in 5 per cent. formalin and examined microscopically.

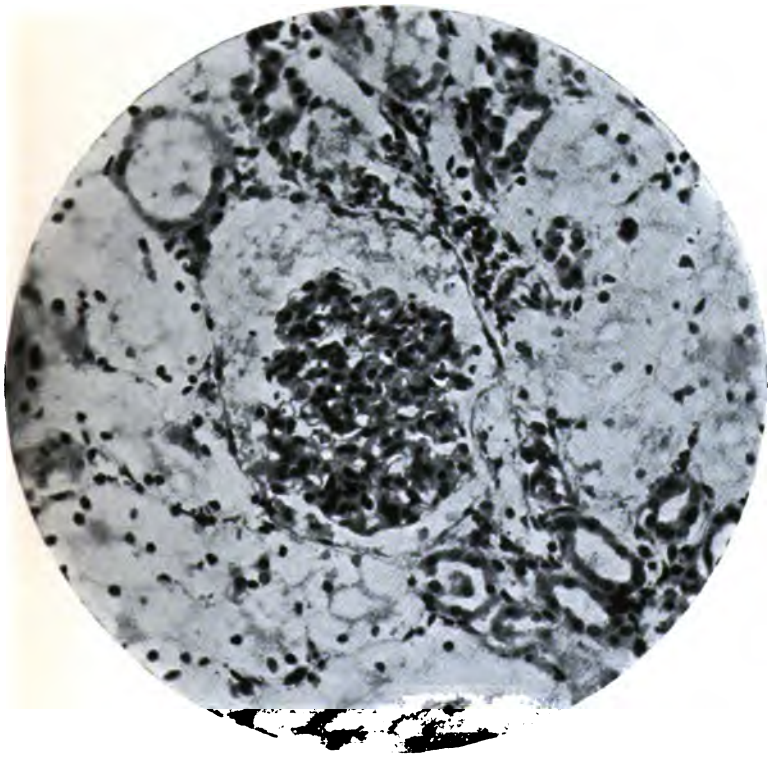
Microscopical Examination of Kidneys. After the malarial infection was suspected on account of the peculiar pigmentation of the glomeruli and straight vessels, thin sections cut in celloidin and paraffin were stained most successfully by Nocht's method as employed for blood-smears. This was the only method by which I could secure a blue color in the bodies of parasites lying in red cells stained deeply by eosin. For this purpose sections remained in the dye for twenty-four hours, and were then slightly decolorized in alcohol and cleared in oil of cajuput. The chromatin, however, was not usually stained. The changes demonstrated by this and other methods were of a most remarkable type.

The lining cells of the convoluted tubules were almost entirely destroyed, not by erosion, but by extreme swelling and degeneration, apparently of hydropic type. (Fig. 1.)

These tubules were thereby distended and uniformly filled by an indiscriminate mass of vacuolated cell detritus in which pyknotic nuclei were irregularly scattered. All the cortical tubules were about uniformly affected. The glomeruli contained a moderate number of pigmented cells and a few parasites within the capillaries, while the capsules were distended by granular coagulum. The small cortical vessels were almost invariably collapsed, and to this perfectly bloodless condition must be ascribed the whitish color visible in the gross. Occasionally a capillary was found distended with a mass of pigmented parasites.

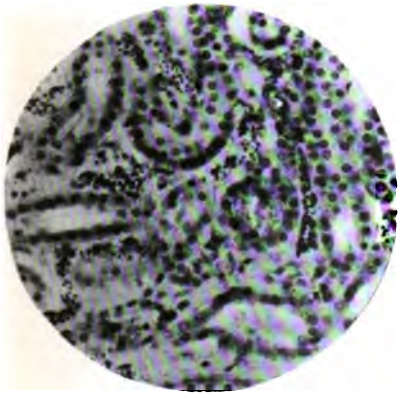
In the medulla the lining cells of all tubules were markedly eroded. In this region most of the capillaries were filled, and many were distended with masses of infected red cells and pigmented parasites which had nearly destroyed the red cells. (Fig. 2.) Many of the distended capillaries were ruptured, and the tissue was studded with miliary hemorrhages, about some of which a few leukocytes, mostly mononuclear, were gathered. The parasites were of small and very uniform size, but richly pigmented. They were identical in appearance with the full-grown forms of the estivo-autumnal parasites seen in sections of tissues of other cases in which these parasites were identified in the blood during life. Very few rings or rosettes could be discovered, so that the brood was unusually compact. (Fig. 3.) Their numbers and compact massing were similar to what I have seen in other fatal cases in which the parasites were massed in the brain, heart muscle, or bone-marrow. The discharging tubules were distended with casts, usually coarsely granular, sometimes entangling infected red cells and pigmented leukocytes. Some infected red cells lay free in the lowest discharging tubules.

FIG. 1.



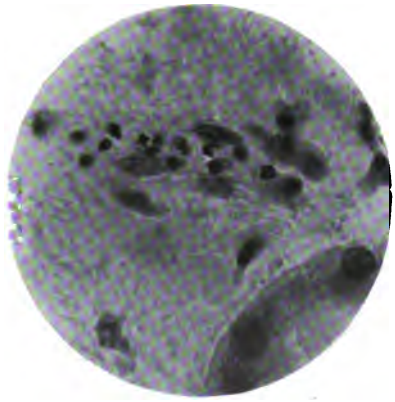
Convoluted tubules and Malpighian body. × 250.

FIG. 2.



Malarial parasites in kidney. × 250.

FIG. 3.



Parasites in renal capillary. × 1000.

The infarcted area in the right kidney was in an early stage of coagulation necrosis. All the capillaries about this area and many within it were distended with blood cells, most of which contained parasites and pigment. Many of the vessels leading to this area were distended to two or three times their natural caliber by thrombi of infected red cells. The infarction is clearly referable to the plugging of small vessels, mostly capillaries, by thrombi of infected red cells. The number of parasites in this cortical zone and throughout this section of the medulla was greater than I have ever seen in any other tissue.

The following summary presents the lesions observed in the kidneys: Extreme and peculiar degeneration of lining cells of all cortical tubules. Distention of capsules of glomeruli by granular albuminous coagulum. Occlusion of most cortical capillaries by the distended tubules. Large superficial red and white infarction, from occlusion of vessels by thrombi of infected red cells. Numerous miliary hemorrhages from rupture of distended capillaries. Distention of nearly all capillaries in the medulla and papillæ by infected red cells and parasites. Casts in discharging tubules, consisting usually of coarsely granular material, but sometimes entangling infected red cells and pigmented leukocytes.

Epicritical. The following questions arise concerning the significance of the above findings:

1. Is it possible to draw any conclusions regarding the significance of the renal lesions on account of the failure to examine the other viscera microscopically?

2. Is the present case a true example of massing of estivo-autumnal parasites in the kidney comparable to the cases in which they have been found massed in the brain in comatose cases, in the gastro-intestinal tract in choleraic cases, in the heart muscle in cardiac cases, or in the marrow, as observed in a case of pernicious anemia?

3. What is the origin of the extreme degeneration of the cortical tubules?

1. To the first question there can be no hesitation in answering that the renal lesions are in themselves sufficiently distinct to stand as the chief feature of the case. Doubtless there were many parasites in the other viscera, but where pigmented parasites are extensively massed in any tissue gross evidence of their presence may be detected in the excessive pigmentation and extreme blood content of that tissue. No such evidence being present in the gross appearance of any other viscus, it is safe to conclude not only that the kidney contained an excessive proportion of parasites, but that they were not excessively

numerous in any other locality. The clinical features of the case also support this belief.

2. It is equally clear that the case is one of true malarial nephritis in which a peculiar hemorrhagic character of the lesion is referable to the mechanical effects of massing of parasites in the renal tissue. This lesion is not to be classed with the usual type of renal lesion in malaria, which is an acute degeneration referable to the general toxemia of the disease, and in which comparatively few parasites have heretofore been found in the kidney. Enormous numbers of parasites in the capillaries, thrombosis of many vessels, and multiple hemorrhages are the specific lesions observed when the parasites have been massed in the brain, gastrointestinal tract, heart muscle, and marrow.

3. The extreme degeneration of the cortical tubules seems also to be a somewhat peculiar feature of the present case. In the reported cases of malarial nephritis of purely toxic origin the degeneration of tubule-cells has often been extreme, but it has always been of a different type from that described above. In fourteen cases which I have examined the degenerative changes have always been much less advanced and of a different type from those of the present case. Although much of the change in the tubule-cells was doubtless owing to the general toxemia of the disease, I am inclined to refer the peculiar character of the process and its extreme degree to the presence of so many parasites in the tissues acting principally through obstruction of the circulation.

Finally, it is important to consider the possibilities of diagnosis during life of this type of malarial nephritis. From the clinical examination of the urine and the microscopical appearance of the discharging tubules in the kidney, it seems probable that a diagnosis of this type of malarial nephritis may be established during life on the following evidence, to be obtained from the urine: Partial or complete suppression of urine; considerable admixture of intact red cells; a considerable proportion of albumin; the presence of many coarsely granular, epithelial, and some blood casts; the presence of *infected red cells*, both free and adherent to casts, and of pigmented leukocytes adherent to casts.

The present case, while demonstrating the existence of a specific type of malarial nephritis, yields no new indication why the estivo-

autumnal parasite selects certain viscera for its chief attack, and demonstrates no new character in the pathogenic action of this protozoon.

There is no known reason why the bronchopulmonary mucosa, or that of the colon, or the serous membranes, or the skeletal muscles, should not suffer in the same way as do the brain, the gastrointestinal mucosa, the heart muscle, and the marrow. The kidney may be specially exempt on account of its rapid circulation, as suggested by Guarnieri, but apparently it does not always escape. The actively phagocytic viscera, the liver and spleen, seem capable of rapidly destroying the enormous influx of parasites which frequently reach their capillary systems. Yet the marrow, with its more complex circulation, is known to be less resistant than the spleen and lymph nodes.

These two factors, however, rapid arterial circulation and active phagocytic powers, seem to be the only qualities which can preserve a tissue from occasional overwhelming growth of the estivo-autumnal parasite.

Microscopical examination of the kidneys of fatal cases of malaria has, then, yielded evidence of three main types of acute renal lesions occurring in this disease.

1. Acute degeneration of toxic origin, often reaching a degree in which exudation of blood-serum into the tubules is added. This lesion is responsible for the vast majority of the cases of albuminuria in malaria.

2. An extreme form of acute degeneration, with focal necroses, numerous hemorrhages, and exudation into the tubules of blood-serum and blood-pigments. This lesion is seen in cases of hemoglobinuric malarial fever, and it has not yet been found associated with an excessive number of parasites in the capillary vessels.

3. Massing of parasites in the renal capillaries, with extreme degeneration of parenchyma cells, multiple hemorrhages, and exudation of blood-serum into the tubules. It seems certain that this type of lesion can occur only in severe estivo-autumnal infections.

There is anatomical evidence that in the pernicious estivo-autumnal cases the three types of lesions may be variously combined, but no good reason for believing that with the benign tertian infection occurring in this latitude any other than the first type can exist.

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ON THE CLINICAL ASPECTS OF PLAGUE.

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As the time allotted to this discussion is necessarily limited to a few minutes, I shall confine my remarks chiefly to the characterization of the clinical types of plague and to the diagnosis of the disease rather than enter upon an analysis of the individual symptoms. The statements are based upon a clinical study of plague made in San Francisco[1] in February, 1901, and previously in 1899,[2] in Hong Kong and in India (Bombay, Poona). The descriptions are based upon the conception that plague is a disease due to infection with a bacillus (B. pestis), which is capable of causing acute general septicemia without visible local reaction in highly susceptible animals, or a local process (usually manifested in the nearest lymph glands rather than at the site of inoculation) in resistant animals, or processes intermediate in severity in animals intermediate in resistance.

The first case of plague was discovered in San Francisco on March 6, 1900, by Drs. F. P. Wilson and W. H. Kellogg, the diagnosis being confirmed by animal experiment by Dr. J. J. Kinyoun, of the United States Marine Hospital Service. There are indications that the disease has existed even longer, but the proof for this can scarcely be brought. In all probability it came to San Francisco from Hong Kong or Canton, and is accordingly to be looked upon as an offshoot of the Chinese epidemic.

The disease in San Francisco has at no time prevailed in the form

[1] As a member of a Commission appointed by the Secretary of the Treasury under the orders of the Surgeon-General of the Marine Hospital Service.

[2] As a member of a Commission sent by the Johns Hopkins University to study tropical diseases in the Philippine Islands.

of an outspoken epidemic, the mortality tables not being conspicuously altered by its presence:

MORTALITY FROM ALL CAUSES AMONG CHINESE OF SAN FRANCISCO, 1897–1901.

Months.	1897	1898	1899	1900	1901	Months.	1897	1898	1899	1900	1901
January,	37	35	46	64	45	August,	35	47	43	19	
February,	46	36	39	48		September,	45	27	35	27	
March,	38	46	37	47		October,	36	53	44	32	
April,	35	41	33	30		November,	39	66	37	34	
May,	27	34	36	42		December,	23	46	48	32	
June,	30	21	46	25							
July,	39	25	34	38		Total,	430	477	478	438	45

On the contrary, the progress of the disease in California has been that which has characterized plague before the outbreak of a great epidemic in nearly every place where the disease has prevailed. It is the same kind of "sneaking" progress as was seen in Hong Kong, Calcutta, and Bombay for months before large numbers of people were attacked. That such "sneaking" epidemics may die out without culminating in a large outbreak was demonstrated by the experience in Ahmedabad from October, 1896, to August, 1897, where, though one hundred and thirty-six cases of plague were imported, the disease developed in only twenty-seven of the inhabitants.

In connection with the fact that no great outbreak has occurred in San Francisco, it is significant that as far as ascertained there has been no general infection of the rats of that city. A small number of rats found dead, as well as several living rats caught in the sewers of Chinatown, showed no evidence of infection with bacillus pestis.

Up to the time of our visit to San Francisco twenty-five deaths due to plague had been discovered during a period of about eleven months (March, 1900, to January, 1901). These cases have been reported by Dr. Kellogg,[1] and it is from his reports that I have drawn the data

[1] Kellogg, W. H. The Plague: Report of Cases, Occid. Med. Times, S. F., 1900, vol. xiv. pp. 197–207. Kellogg and Kinyoun. J. J. The Plague: Thirteenth Case, ibid., 1900, vol. xiv. pp. 245–257. Kellogg, W. H. Plague Cases Fourteen and Fifteen, ibid., 1900, vol. xiv. pp. 284–85. The Plague in San Francisco, Cases Sixteen, Seventeen, and Eighteen, ibid., 1900, vol. xiv. pp. 345–47. Plague in San Francisco, ibid., 1901, vol. xv. pp. 11–15. Plague Cases Twenty-three, Twenty-four, and Twenty-five, ibid., 1901, vol. xv. pp. 45–46.

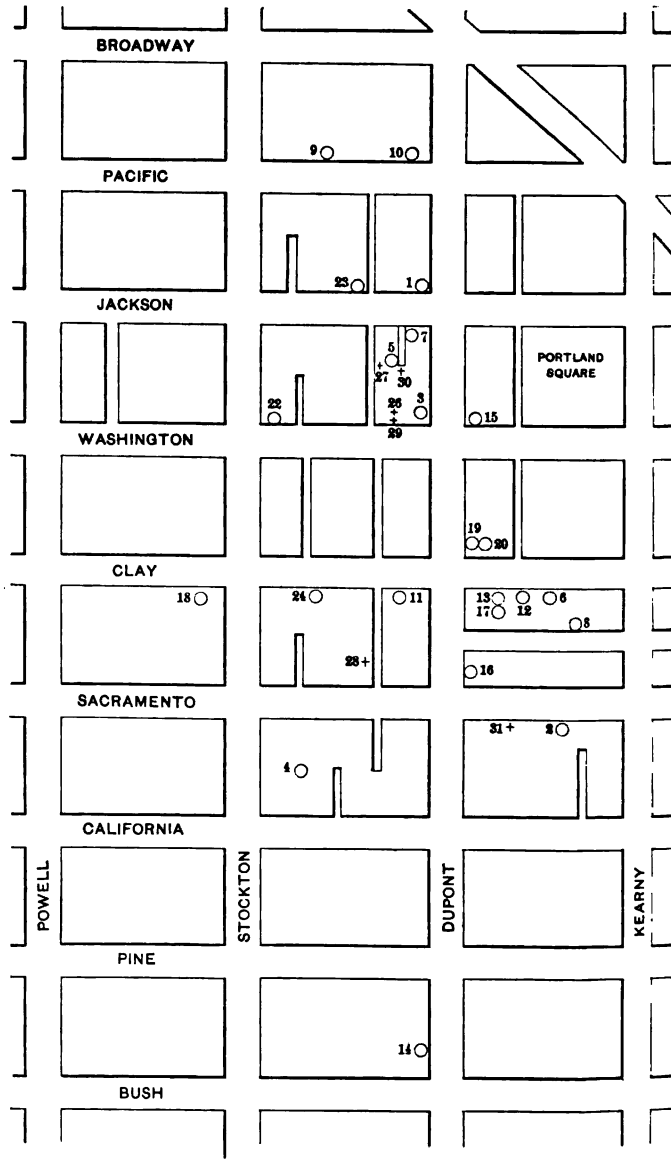
referable to the cases which occurred before February, 1901. During the eight days—February 6 to February 13, 1901—the special Commission from the Treasury Department found six cases of plague. Altogether, then, from March 6, 1900, to February 13, 1901, thirty-one cases of plague had been recognized. Most of them were found dead, and the diagnosis was based upon the pathologic appearance and the bacteriologic examinations. Several cases were, however, studied during life. Of the six cases observed by the commission, three were seen during life, and two of these three recognized clinically as cases of bubonic plague.

No.	Name.	Age.	Sex.	Color.	Place of death.	Date of death.
1	Wing Chut King,	41	M.	Mongolian,	1001 Dupont,	Mar. 6, 1900
2	Chu Gan,	22	"	"	723 Sacramento,	" 15, "
3	Ng Ach Gin,	37	"	"	905 Dupont,	" 17, "
4	Lee Sun King,	47	"	"	Oneida Place,	" 18, "
5	Law An,	38	"	"	St. Louis Alley,	Apr. 24, "
6	Lim Fa Muey,	16	F.	"	739 Clay,	May 11, "
7	Chu Sam,	38	M.	"	717 Jackson,	" 11, "
8	Chin Moon,	16	F.	"	730½ Commercial,	" 13, "
9	Her Woon Jock,	53	M.	"	740 Pacific,	" 14, "
10	Dang Hong,	40	"	"	706 "	" 29, "
11	Chen Kney Kim,	49	"	"	819 Clay,	June 2, "
12	Jay Man Tong,	60	"	"	759 "	" 9, "
13	Lee Wing Tong,	40	"	"	767 "	July 6, "
14	William Murphy,	34	"	White,	427 Dupont,	Aug. 11, "
15	Ham Tan,	29	"	Mongolian,	900 "	" 15, "
16	Lee Do Hen,	50	"	"	710½ "	Oct. 5, "
17	Chun Yen,	37	"	"	767 Clay,	" 10, "
18	Talk Dong Leong,	39	"	"	705 "	" 14, "
19	Young Moon Li Chee,	30	F.	"	802 Dupont,	" 31, "
20	Young Wah Noui,	9	"	"	802 "	Nov. 1, "
21	Anne Roede,	28	"	White,	Pacific Hospital,	" 3, "
22	Lee Ho,	30	M.	Mongolian,	844 Washington,	Dec. 7, "
23	Chun Wey Lung,	60	"	"	780 Jackson,	Jan. 6, 1901
24	Leam Wing Low,	59	"	"	633½ Clay,	" 15, "
25	Angela Colombo,	...	"	White,	5 Lafayette Place,	" 15, "
26	Chun Ah Chou, *a*	44	"	Mongolian,	814 Washington,	Feb. 5, "
27	Lum Hong Yuen, *a*	37	"	"	28 Ross Alley,	" 6, "
28	Wong Chi Lui, *a*	50	"	"	15½ Waverley,	" 7, "
29	Tom Shom, *a*	51	"	"	814 Washington,	" 10, "
30	Ung Ah Buck, *a*	45	"	"	St. Louis Alley,	" 11, "
31	Foong Ah Fong, *a*	12	F.	"	747 Sacramento,	" 12, "

a. Observed by Commission.

NOTE.—Particular places of death of following numbers were as indicated below: No. 8, Pacific Hospital, Stockton and Chestnut Streets; No. 13. City and County Hospital; No. 14, City and County Hospital; No. 21, Children's Hospital, 3700 California Street; No. 25, City and County Hospital.

The accompanying map (page 462) shows the distribution of the plague cases in San Francisco:



Map of "Chinatown," San Francisco.

Circles indicate cases seen and regarded as plague by City Board of Health before arrival of Commission.

Crosses indicate cases of plague observed by the Commissioners from February 5th to February 12, 1901.

Of the thirty-one cases, twenty-eight were Mongolians and only three Caucasians. As to age, the following table gives the deaths according to decades:

Age.	Deaths.
1 to 10 years	1
11 " 20 "	3
21 " 30 "	5
31 " 40 "	9
41 " 50 "	7
51 " 60 "	5
61 " 70 "	0

As is well known, plague usually kills more people between twenty and thirty than in any other decade. It is to be remembered, however, that in San Francisco the Mongolian population may scarcely be regarded as a normal one. The number of females is small, there are relatively few births in Chinatown, and relatively few young people. The predominance of male and middle-aged individuals is easily explicable when the legal status of the Chinese in America is considered.

Of the thirty-one cases, six were in females and twenty-five in males. Experience in other epidemics indicates that there is but little difference in the number of males and females attacked. The disproportion in the San Francisco epidemic is doubtless dependent upon the small number of female Chinese living in Chinatown.

The type of the disease which has been prevailing is the bubonic. In twenty-three of the thirty-one cases a definite bubo (probably primary) was made out in twenty-three instances. Only one primary septicemic case was established, and only one pneumonic case was observed. In seven of the cases the descriptions do not permit of definite classification as regards the clinical type, though the diagnosis of the disease itself was in each case fully established.

The daily inspections of the sick and dead permitted of observations relative to the mode of life of the people in the fourteen blocks of San Francisco which make up "Chinatown." These observations were extended by special trips of inspection under the guidance of officers of the city detective force and by numerous independent trips of inspection.

The dwellings of the poorer classes of Chinese were found to be here, as they seem to be everywhere, shockingly unsanitary. In

places there is marked overcrowding; the rooms are small; they are often entirely devoid of light or means of ventilation, and nearly always insufficiently lighted and ventilated; many of them are filthy; some of them, especially those situated in basements, are damp, and emit a foul stench. These faults in sanitation are not confined to the tenement-houses of the Chinese; on the contrary, in the rear of or over or under some of the more pretentious business dwellings are to be found sleeping and living apartments which are most objectionable from a sanitary point of view.

The Chinese in San Francisco are, however, in many respects much better off than are their countrymen in great native centers like Canton, or even than those in a city like Hong Kong. There is almost an entire absence of the utter destitution met with among many of the Chinese in Asia. The Chinese in San Francisco are, on the whole, very well fed, for wages are high and food is abundant and cheap. They are also well clothed, as a rule, and particular emphasis is to be laid upon the fact that the Chinese here wear shoes, stockings, and trousers, since it is believed by many that the bare legs and feet of the Chinese in Hong Kong and Canton had much to do with the frequency of infection with plague in those places.

A large percentage of the Chinese in San Francisco, it is said, smoke opium. There are a number of Chinese prostitutes, but inspection of the quarters occupied by the latter would indicate that the rooms in which they live are, on the whole, more wholesome as regards air-space, light, ventilation, and cleanliness than those of the other inhabitants of the district.

The Bubonic Cases or Glandular Plague.

The ordinary clinical features of this form are now so familiar that they need scarcely be entered into in detail. The symptom-complex is characteristic, and there ought to be but little difficulty, as a rule, in making a diagnosis. The sudden onset of fever, preceded. usually, by but few prodromata, associated very quickly with painful glandular enlargements, severe headache, nausea, and vomiting are the conditions commonly met with. The fever varies between 103° and 105° F., but may rise as high as 108° or even higher. There is a moderate leukocytosis associated with some anemia, and with a moderate diminution in the amount of hemoglobin.

The buboes usually appear rapidly after the first onset of symptoms. Indeed, if a physician is called he nearly always finds a bubo already developed. The size varies according to the stage of development of the bubo and the character of the infection. Usually one gland of a group swells first, after which there is rapid extension to other glands of the packet. The larger buboes are due to swelling of several glands and edema of the adjacent tissues. In the fully developed buboes it is usually impossible to make out the individual glands of which the whole swelling is made up. The buboes are exquisitely painful, as a rule, though some lethargic patients complain but little. They are especially sensitive on pressure. Among the Chinese it was common to find a black plaster applied to the region of the swollen glands, to alleviate what the patient regarded as "rheumatic" pain. A good deal of stress is to be laid upon the elastic resistance of the swelling, which is due to the edema. The skin may be tense over the swelling; it looks thin and glossy. It is often reddened over the bubo, and occasionally vesicles or pustules appear on the surface. In very large buboes, especially in the cervical region, the jelly-like trembling which has been described can easily be made out. If the edema becomes very extensive the bubo may be obscured. Most patients assume the attitude best calculated to relieve the tension in the region of the bubo; thus, where the bubo is inguinal the leg is flexed at the knee and the thigh moderately flexed and rotated outward.

As Müller and Pöch have pointed out, the clinical classification of buboes differs of necessity somewhat from the classification based upon the pathology of the disease.[1] The pathologists distinguish primary buboes of the first order, primary buboes of the second order, and secondary buboes, the first group including the buboes appearing in the glands nearest the site of inoculation, the second group including the buboes formed by extension of the bacilli directly through the lymphatics from the primary bubo to a second adjacent group of lymph glands, and the third group including buboes arising through the deposition of bacilli from the circulating blood in the lymph glands in any part of the body. Clinically, it may be very difficult or impossible to distinguish primary buboes of the second order from secondary buboes. We are reduced to distinguishing the "clinically

[1] See Dr. Flexner's report.

primary" bubo from the "symptomatic" bubo. The clinically primary bubo is nearly always a primary bubo of the first order. The symptomatic buboes may be primary buboes of the second order or true secondary buboes.

In a suspected case of plague it is necessary to search widely for a primary bubo. If it is not easily found, one should examine every part of the body in which lymph glands are situated before concluding that no primary bubo is present. It is probable that there are some primary buboes too small to be recognized clinically, though it is more likely that in many instances the smaller buboes which could have been detected by careful search have been overlooked. In the bubonic form death occurs usually in from four to six days. In San Francisco we got histories of a much longer duration in several cases. Where the disease is prolonged suppuration may occur. A striking feature of the disease is the absence of lymphangitis between the site of inoculation and the lymph gland attacked. It is rare that one can make out the point of entrance of the virus, though occasionally a vesicle or a pustule exists, the so-called primary skin lesion in the bubonic form of the disease.

The inguinal type of glandular plague was much more common in San Francisco than the axillary and cervical types, and this is in accord with general experience. As an example of typical inguinal bubonic plague, the following instance may be cited:

Tom Shom, male, aged fifty-one years, actor in Chinese theatre; room above theatre at 814 Washington Street, near the room of late Chun Ah Chou (see death 26). This man was reported as ill to the Six Companies, and was examined clinically on Friday, February 8th, by the writer, who obtained the following history: The man had been acting in the theatre about two weeks before, although it had been stated that he had not been very well for from six to seven months previously. On February 4th he became seriously ill with fever and delirium. There had been some vomiting. The urine, as observed by the attendant, was described as brandy colored. He had a Chinese doctor in attendance, and his friends had not considered him ill enough to make a report to the Six Companies worth while. The man smoked about fifty cents' worth of opium daily. On clinical examination the patient was found lying upon his back in bed, with legs drawn up; he was in a state of semistupor. His pulse was 108, quick, rather full, but of low tension. The skin was hot and dry; respiration 20 to the minute. The face had an anxious expression; the tongue was coated in the middle. There was no palpable enlargement of the glands of the neck or axillæ, but in the

right groin several slightly enlarged glands could be distinctly felt, and the patient, though his mind was partially clouded, winced decidedly when either groin was palpated. It was evident that the glands were quite tender. In the absence of urethral discharge, chancre, or evidence of local irritation in the lower extremities, the case was, on account of the local and general phenomena, regarded as one of plague. The skin was cleansed and a sterilized hypodermic needle introduced into the groin. A few drops of bloody fluid were withdrawn, presumably from one of the enlarged glands. It was difficult to be sure of this, however, as the patient could not be kept quiet while the needle was being inserted. No colonies of plague bacilli developed in the inoculated tube. The necropsy, subsequently made, indicated that the needle had failed to enter an enlarged gland.

The patient was seen on the following day, when his condition showed no change for the better. The pulse was 136 and feebler, the patient seemed in general weaker, and an unfavorable prognosis was made. The patient's friends were told that an injection of Yersin's serum offered the best chances for recovery, though they were also told that not much could be hoped from any treatment in the stage of the disease in which the patient then was. The offer was refused. The man died on February 10th, the next day.

The dead body was inspected on the morning of February 11th. The body was in a state of firm rigor mortis, the limbs being strongly flexed. On breaking down the rigor mortis and palpating the glands in the groin, it was difficult to say positively that there was any enlargement of the lymphatic glands. In view of the enlargement distinctly made out during life and the clinical picture which had been observed, the death was believed to be one due to plague, and a pathologic and bacteriologic examination undertaken.

At autopsy there was a slight swelling in the right inguino-femoral region which, on incision, revealed slightly edematous subcutaneous tissue, with slight enlargement of the glands. The largest gland was the size of a filbert, and its surface was dark and hemorrhagic; on section, it presented distinct hemorrhages; other glands were swollen, soft, juicy, and hemorrhagic. The spleen was enlarged, soft, and friable. The examination of the groin showed that the hypodermic puncture made for the withdrawal of fluid for diagnostic purposes during life had failed to enter a lymph gland.

Cover-slips from the spleen and glands showed large numbers of bacilli having the characteristic properties of the B. pestis.

Sometimes these inguinal cases are associated with a marked hemorrhagic diathesis. This existed in the case of W. M.,[1] who died on August 11, 1900.

M. was a white man, aged thirty-four years, who on August 7, 1901, complained of pain and slight swelling of the right groin, followed by nausea, general soreness, headache, and vomiting. He had albumin in his urine, his

[1] See Dr. Kellogg's report.

temperature was 100°, pulse 100, and the bubo in the right femoral region became rather painful. He died on August 11th. Autopsy by Prof. Taylor. Two enlarged lymph glands were found in the right groin. These were hemorrhagic, but not purulent. The femoral glands were also enlarged. The plague bacillus was present in smears made from the glands, and animals inoculated therefrom died with typical plague lesions. The mesentery was mottled with hemorrhages. The walls of the stomach were markedly injected, and there were submucous hemorrhages in this organ. The spleen was very friable. Extensive hemorrhages were found about the pancreas, in its substance, and in the lesser peritoneal cavity. There was no fat necrosis.

Axillary buboes were not met with during the stay of the commission in San Francisco, nor do they appear to have been seen by San Francisco clinicians. In view of the experience in India and China, where axillary buboes are much more common than cervical buboes, it would seem possible that the axillary buboes, possibly of small size, had been overlooked in some cases in San Francisco. Axillary buboes are, however, more common in women than in men, and the small number of women in San Francisco may have had something to do with the non-discovery of axillary buboes.

Cervical buboes come next in frequency. They are usually very large and painful. The edema is extensive, and there is often difficulty in swallowing. A typical case was seen by the Commission on February 12th:

Ung Ah Buck, aged forty-five years, found dead at Wing Hai's undertaking establishment, on Sacramento Street. This man had been seen alive and examined by the writer on the previous day, who diagnosed the case, *intra vitam*, as one of cervical bubonic plague. When seen alive he was in a room upstairs in the rear of 921½ Dupont Street, opposite St. Louis alley. The man was sitting up, but looked extremely ill. His face was pale, cyanotic, and anxious-looking. His voice was very feeble, but his intelligence seemed almost unclouded, and he was able to carry on a conversation, though with difficulty, with the interpreter. The friends stated that he had at times wandered in his talk. He was under the care of Dr. Mather. The patient stated that he had been ill for two weeks. His neck had been swollen for one week, and he regarded the condition as quinsy. With the aid of a tongue depressor the throat was examined. The fauces were swollen and reddened, the swelling being very marked in the left side. The left palatine tonsil was much enlarged and showed on its surface a grayish-white patch the size of a dime. The reddening in the throat was general, and there was less local injection than one ordinarily sees in diphtheria. The left side of the neck was brownish-yellow, having been painted over with a solution of iodin. On inspection

and palpation marked bulging was found. This seemed to be due to enlargement of the cervical lymphatic glands. The case was diagnosed as one of plague, with cervical bubo. The man died the next day, and a complete autopsy was made by Dr. Flexner. The pathologic examination showed typical lesions of plague, and the bacteriologic examination made by Dr. Novy demonstrated the presence of B. pestis.

Autopsy, February 12th at noon, at the undertaking shop of Wing Hai by Dr. Flexner, Drs. Novy, Barker, Kellogg, and Wilson being present. The left side of the face and neck presented a marked diffuse swelling, extending from the angle of the jaw backward to the sternocleidomastoid muscle and below, almost reaching the clavicle.

On incising this region the parotid gland was first reached; this organ presented a normal appearance. After dissecting away the parotid gland a group of greatly enlarged deep glands surrounding the carotid artery and jugular vein came into view. The periglandular tissue was infiltrated with bloody fluid and presented a sodden appearance. The enlarged glands and portions of the surrounding tissue were excised; the former were found to be swollen (several reaching the size of an English walnut) and to be wholly altered in appearance and consistence. In color they were deep purplish, and on incision a hemorrhagic fluid exuded. Opaque points of necrosis were also present.

The general subcutaneous fat was well developed; there was no general edema. Peritoneum appeared smooth and glistening; there was no excess of fluid in the abdominal cavity, and the abdominal glands were not noticeably swollen. The spleen was enlarged to fully twice its normal size; it presented a purplish color, and its consistence was diminished. The pleural cavities were dry. The lungs retracted moderately upon removal of the sternum. The lower lobes of the lungs were congested, but no consolidation was made out. No other abnormality was observed in the body.

The organs and tissues removed at this necropsy, consisting of the enlarged cervical glands and spleen, were taken to the laboratory, where cover-slips, cultures, and animal inoculations were made.

The cover-slips from the spleen showed large numbers of a bacillus having the morphology and staining properties of the B. pestis. The cover-slips from the glands differed in their appearance. In some instances there were present large numbers of bacilli similar to those in the spleen, together with a few diplococci or short chains of cocci. Other cover-slips showed, beside the organisms mentioned, a bacillus having the morphology of the B. diphtheriæ. Animals inoculated died with typical plague lesions, and pure cultures of the B. pestis were obtained from them.

Cubital and popliteal buboes were not met with in San Francisco.

Symptomatic buboes were seen in several cases. On autopsy these proved to be in some instances primary buboes of the second order, in other instances true secondary buboes.

The Septicemic Cases.

The more one studies plague the more he is impressed with the resemblance of plague infections to those which occur in anthrax. It has been doubted by some, among them no less acute an observer than Müller, whether primary plague septicemia occurs without any primary bubo. It is easy to say when no primary bubo is found in a case of plague septicemia that the pathologist has overlooked the primary bubo at autopsy, but autopsies have been made by very careful pathologists in which no definite primary bubo could be made out. And it would seem that we are as much justified in assuming the existence of a primary plague septicemia as of any other form of primary septicemia. Terminal plague septicemia in fatal cases of the bubonic form, and probably of other local forms of disease, is far more common. Between a plague septicemia, primary from the first, and the terminal plague septicemia secondary to primarily localized plague infections, various transition forms are met with.

Primary Plague Septicemia. One can think of the bacillus getting into the blood in cases of primary plague septicemia in various ways. When a human being or an animal is extremely susceptible it is conceivable that the bacillus could enter through the skin and pass through the lymph glands, and so into the blood without setting up a primary bubo. In the same way it could enter through the conjunctiva or other exposed mucous membranes. It is possible that entrance could occur from the respiratory tract without setting up local pulmonary lesions other than a mild bronchial catarrh, and, finally, direct infection of the blood through the bites of insects may be thought of.

In primary plague septicemia the clinician has to deal with the phenomena of general septic infection; the fever is high, the pulse is frequent and feeble; there may be delirium and coma. A splenic tumor rapidly develops, and is often associated with acute pain in the left side. There is tenderness over all the lymph glands of the body. Frequently there are hemorrhages into the skin or from the mucous membranes of the lungs, stomach, intestines, or urinary passages. In such cases the bacilli can frequently be found in cover-slips made from the blood; cultures from the blood are, however, more reliable for the discovery of the bacilli, and animals inoculated with a few cubic centimeters of blood die with typical lesions of plague. These primary

septicemic cases include many of the frightfully acute infections met with in large epidemics; death may occur in from one to three days from the time the patient is first attacked or even after the lapse of a few hours.

In San Francisco a white nurse died of what appears to have been this form of the disease. She was taken suddenly ill, complaining of severe pain all over the body. Her temperature was 40° C., pulse 104, respiration 33. There were hemorrhages from the urinary passages and the sputum was blood-stained. Hemorrhagic petechiæ were found about the elbows and ankles. She died in the hospital, and an autopsy was made by Dr. Harold Bruhn. The inguinal glands were slightly but not markedly enlarged. The axillary and cervical glands were not large. There was some free blood in the pelvic peritoneal cavity. In the mesentery the glands were slightly enlarged. No pulmonary lesions were found. The spleen was enlarged and softened. There were subperitoneal hemorrhages, and submucous hemorrhages in the intestine. The pathologic diagnosis was septicemia, with tendency toward minute hemorrhages in the tissue. Bacteriologic examination proved that the blood was full of bacilli of plague, and there were enormous numbers of the plague bacilli in the spleen.

Secondary Plague Septicemia. It seems likely that in nearly all cases of bubonic plague at least a few bacteria get over into the blood. It is these which account for the true secondary buboes which are regarded by the pathologists as being embolic in origin. In many of the fatal cases of bubonic plague the bacteria go over into the blood and multiply in great numbers, so that the blood and spleen at death and shortly before contain large numbers of the plague bacilli. In cases of the bubonic form of the disease which recover it may be that such a general bacteremia does not occur, the process remaining essentially localized to the primary buboes, or, if a few bacilli get over into the blood, they are filtered out by the organs, and give rise to either secondary buboes or to no noticeable phenomena.

Plague Pneumonia.

Primary plague pneumonia is to be distinguished from the secondary pneumonias which occur in the course of other forms of infection with plague. By primary plague pneumonia is understood that form in which the bacillus gains entrance to the body through the respiratory tract, and sets up a definite primary pneumonia, usually lobular, but sometimes pseudolobar in form.

Under the term secondary plague pneumonia are to be included:

(*a*) Pneumonia due to embolic infection of the lungs with plague bacilli in cases of bubonic plague or plague septicemia.

(*b*) Ordinary bronchopneumonias complicating plague as they do other grave infections—*e.g.*, aspiration pneumonia and the like. The bronchopneumonias of this group are most often due to infection with the streptococcus or the micrococcus lanceolatus. Occasionally an aspiration pneumonia complicating plague is due to the plague bacillus itself. This is particularly apt to occur if there be ulcerated tonsillar buboes.

The only case of primary plague pneumonia recorded in San Francisco occurred before the visit of the Commission. It is Case No. 20 of Dr. Kellogg's series, a Chinese child, aged nine years, who died on November 1, 1900, at 802 Dupont Street.

In some epidemics primary plague pneumonia is the prevailing form of the disease. This appears to have been the case in the Black Death which spread over Europe in the fourteenth century, and also in the Pali-pest in 1836. Plague pneumonia is undoubtedly frequently overlooked during the course of an epidemic.

It is to Childe, of Bombay, that we owe the establishment of primary plague pneumonia as a definite clinical and pathologic entity. The patient is taken suddenly ill with a chill, stitch in the side, severe headache, and high fever. The clinical phenomena of a grave pneumonia develop. The respirations are increased from 50 to 80 per minute, and signs of consolidation appear. The pulse is frequent and soon becomes very feeble. An acute splenic tumor can be made out. There may be sensitiveness in the region of the various lymph glands of the body. The typical rusty sputum of ordinary croupous pneumonia is but seldom met with. Instead the sputum is actually bloody (hemoptysis) and may be copious in amount. There is usually extreme dyspnea and marked cyanosis.

Nearly all cases of plague pneumonia are fatal, death occurring usually in from one to five days. The duration of the disease may, however, be even longer. During the Black Death it does not appear to have averaged more than two days.

Cutaneous Plague.

Though its existence by some has been denied, it seems clear that *primary* infection of the skin with the plague bacillus is a recognizable

form of the disease. The analogy with anthrax here again becomes evident. The cutaneous lesions take the form of vesicles, pustules, or carbuncles.

When the lesions of the skin are secondary they are usually situated over buboes, and the extension to the skin would seem to be directly by way of the lymphatics from the lymph glands. Embolic infections of the skin may be thought of, but from what we know of the cutaneous bloodvessels they are probably rare.

Primary infections of the skin are certainly very unusual, their absence and the absence of lymphangitis between the point of entrance of the bacilli and the first lymph glands to be infected being characteristic features in the majority of the cases of the disease. A judgment as to the primary or secondary nature of a furuncle or carbuncle has to be based upon the time of its appearance. If it is among the first signs to develop, it may be regarded as a primary lesion; if it appear sometime after the onset of the symptoms, it must be looked upon as of secondary occurrence.

Mild Plague or So-called Pestis Minor.

At the beginning and end of large epidemics it is common to find numbers of cases of plague which are so mild that they cause the patients but little inconvenience; undoubtedly in many instances mild cases pass unrecognized. The severity of cases in any given epidemic appears to conform to a curve. The mild cases in the beginning give place gradually to more and more severe infections until at the acme of the epidemic the most violent septicemic and acutely fatal cases are met with. This stage is followed by a decline in severity until finally the epidemic dies out in a series of mild ambulatory cases. The great importance of these mild cases of plague for the spreading of the disease is obvious. Since the bacilli are given off through the urine and feces an ambulatory case may spread the germs of the disease far and wide. Occasionally an individual who presents what is apparently a mild form of the disease in its early stages may later become very ill. For example, in San Francisco during the visit of the commission one of the fatal cases observed was not considered very ill by his friends in the early part of his attack. Indeed, he walked about and took food with his companions for several days, and it was only shortly before his death that the grave nature of the malady was realized.

There is room for much bacteriologic work upon the epidemics of so-called pestis minor. There have been epidemics described in which as many as two hundred cases of the disease have occurred without a death. One naturally asks the question with regard to such epidemics, Are we dealing here with true bubonic plague or with some other disease? Bacteriologic examination can alone settle the diagnosis in such instances.

Epidemics of so-called "climatic buboes" have been described by various authors (Ruge, Godding, Skinner, Nagel). The exact nature of these climatic buboes is not clear. While some authorities (Cantlie) assume that the disease is an example of a mild, non-fatal infection with the bacillus pestis, there are others (Godding, Scheube) who are just as positive that the disease is essentially different from plague. Here again we are in urgent need of bacteriologic study. It alone will settle this mooted question.

In San Francisco, among the physicians who have been in practice there for some time, great stress was laid upon the "glandular swellings" occurring among the Chinese. It was asserted by some of the most experienced physicians in that city that such glandular swellings had been occurring among the Asiatic inhabitants for no less than thirty years. These physicians were convinced that the cases which were proved by bacteriologic examination to be plague were precisely the same as those of glandular swelling observed in earlier years. In the absence of pathologic and bacteriologic examination of cases of so-called "glandular swelling" of the earlier days, it must for the present remain undecided what the nature of those cases really was.

Of one thing there can no longer be any doubt—the "glandular swellings" occurring among the Chinese in San Francisco in February, 1901, are instances of true infections with the bacillus of bubonic plague.

In all the infections resembling mild cases of plague the importance of bateriologic and pathologic examination for the establishment of the diagnosis is clear. With the help of the naked eye, the microscopic appearance of the lymph glands affected, and of cover-slips, cultures, and animal experiments from the diseased glands, there can be no difficulty whatever nowadays in distinguishing true plague from any other affection.

The Diagnosis of Plague.

In the diagnosis of this disease one will naturally be influenced as to the methods he will pursue by the circumstances under which he is working. If he is to decide as to the nature of the first suspected case in a place where the disease has not hitherto been known to exist, he will be very much more cautious in coming to a conclusion than where he has to pass judgment upon a suspected case in a region in which plague cases are known to be daily occurring. For no conscientious physician will impose upon a community the restrictions as regards travel or the inconveniences and financial loss to commercial interests which the positive diagnosis of plague and the public announcement thereof in a large center entails unless he is absolutely sure of his ground.

The desirability of coming quickly to an absolutely certain conclusion in a *first* suspected case cannot be too strongly emphasized. It is of the greatest importance if plague is breaking out in a community to establish this fact beyond any possibility of question. Owing to the slowness with which plague tends to spread after its first appearance in a place, it is comparatively easy to stamp it out in the bud or limit the spread to a small focus if the very first case be recognized and the proper measures for the prevention of its spread be undertaken. Then, too, it is only when the people of the community are convinced of the presence of a disease which is capable of giving rise to a grave form of epidemic that they will bestir themselves to employ the proper means for the prevention of its spread and for its utter extermination.

In San Francisco the disease was recognized in March, 1900, and its true nature fully established by competent pathologists and bacteriologists. Whether any or how many cases of plague occurred in San Francisco before this date must remain in doubt. The medical men of the city who had had a training in pathology and bacteriology, or who had learned to have confidence in the results of pathologic and bacteriologic work, with a few notable exceptions, concurred in the diagnosis and urged the public to take the appropriate measures for the control of the disease. Unfortunately the matter became a political issue. A certain number of medical men, among them several of prominence, denied the existence of plague, and this, together with

the fact that the disease did not spread to any large extent, helped to encourage the public in thinking that the disease was not bubonic plague—a belief which was heartily in accord with their hopes.

A doubt arose in the public mind as to the possibility of making a certain diagnosis in a suspected case. The people were told that no "living case" had been observed, and that the diagnosis rested purely upon pathologic and bacteriologic examinations. They were further assured that such examinations were insufficient for the making of a diagnosis, and the statement was circulated that bacteriology is "as yet too young a science to interfere in any way with the commerce of a great city."

As a matter of fact, the modern trained physician who has had experience with the disease can make in a case of plague an absolutely positive diagnosis more easily probably than in most of the other infectious diseases. *The diagnosis can be established beyond the shadow of a doubt.* Naturally, when dealing with a first case the most experienced clinician would hesitate to pronounce upon the existence of such a dreaded disease in a community until he had forged a chain of evidence which could not admit of dispute. If he saw the case alive he would subject it to a very thorough clinical examination, would weigh the positive signs with all faithfulness, and would make every effort to exclude the existence of diseases which in any way resemble plague, before deciding that the case was one of pest. If there were buboes, after excluding other possible causes of their origin, he would bacteriologically examine the juices extracted from them by hypodermic syringe. If the patient died he would examine the glands with the naked eye and microscopically, and would make a complete bacteriologic examination of these glands, including animal inoculations.

It is not necessary to have a "living case" before one in order to establish the existence of plague in a city. The pathologic appearances in themselves are absolutely characteristic in the majority of cases, and the bacteriologic examination alone will suffice, if it be positive, for a decision. Fortunate we are that bacteriology, though a young science, has placed in our hands the means of becoming sure whether or not we have among us a disease of such dreadful possibilities as bubonic plague!

It is important, if possible, that men who have had experience with the disease be called upon to give a decision in a suspected

outbreak. Aside from the confidence which the public would repose in the diagnosis under such circumstances, it is undoubtedly true that actual first-hand knowledge of the disease clinically, pathologically, and bacteriologically goes far to make conclusion in a given case quick and easy. The German Government, recognizing this fact, has arranged for definite plague courses at certain of the bacteriologic institutes, where men may be prepared for the special study of the disease. When a suspected case is reported from any source, plague experts with special plague bacteriologic outfits are sent at once to the place, and their report is accepted as final and acted upon immediately.

A large part of the difficulty in San Francisco was due to the non-education of the public and of a portion of the profession with regard to plague matters. As knowledge of plague has increased so rapidly during the past two or three years, and has been so greatly modified during the same period, it is not strange that erroneous views have been and are still in most places prevalent. The idea appears to be very general that if plague once starts in a place it will spread rapidly in the form of a violent epidemic, leading within a very short time to hundreds or even thousands of deaths. Nothing could be further from the truth. It is rare that plague spreads rapidly after the appearance of the first case; it would appear to be only after the rats of the place have become infected that, as a rule, a large outbreak occurs.

The diagnosis in March was made by competent men connected with the City Board of Health and the Marine Hospital Service, and was backed up by the opinion of the professors of pathology and bacteriology in the two best medical schools in San Francisco and by several prominent clinicians. The people of the city and State ran a needless risk in not trusting more fully the conclusions arrived at by the scientific men in their midst.

As a matter of fact, nearly all epidemics of plague begin with cases of the bubonic or glandular form, and this is, fortunately, the form which is most easily diagnosed. If one meets with a number of cases with buboes, occurring in the absence of venereal infection, and associated with severe general symptoms, some of the cases terminating fatally, he may, especially if he be dealing with Asiatic peoples, be almost certain that he has to do with an outbreak of bubonic plague.

One may now and then meet with a septic case without buboes, but, as far as is known, when septicemic cases are occurring in a place there are always at the same time other cases with buboes.

In all doubtful cases, and especially where one is dealing with a *first* case, a thorough bacteriologic examination should be made. This should include the study of the juice from a bubo, if one be present, the sputum, the blood, the splenic juice, the urine, material from skin lesions, and, should there still be doubt, the feces. Cover-slip preparations, cultures, and animal experiments are to be resorted to. It is Dr. Novy's province to deal with the bacteriologic examinations in detail, and I shall, therefore, not enter into the methods here. It is to be remembered that a positive result is of greater significance for diagnosis than a negative one. If no bacilli are obtained from the juice of a suspected bubo one should not stop with the first trial, but should make repeated examinations until the case is clear. Where the disease is epidemic it is unnecessary, in the majority of instances, for diagnostic purposes to go beyond the cover-slip preparation of the juice of a bubo. If this is positive as regards the presence of the plague bacillus, one need go no further. He who is familiar with the clinical symptoms of plague and with the appearance of the plague bacillus under the microscope will not require to make cultures or animal experiments if, in connection with suspicious clinical symptoms, he finds great numbers of the characteristic bacilli in his cover-slip preparations made from the juice of a bubo. If there be any difficulty as to the diagnosis, cultures, and especially inoculation of guinea-pigs, will remove all doubt.

The serum reaction in plague would seem to be of but little value for diagnosis except, possibly, to indicate that an individual has had plague at some time previously, for during the first week of the disease, according to Zabolotny, a positive agglutinating reaction is not obtainable. Since in the majority of fatal cases death occurs from the fourth to the sixth day, the uselessness of the reaction for diagnostic purposes is obvious.

Plague may be confused in certain instances with malaria, typhoid fever, relapsing fever, venereal buboes, and other forms of adenitis. Mistakes are not likely to be made, however, if clinicians resort in every case they examine to a thorough routine clinical study of all the features presented. If malaria exists, the parasites should be

found in the blood. If the case is one of typhoid fever, in the majority of instances the Widal action will be positive. If it is one of relapsing fever, the spirochetæ may be observed microscopically. It is to be remembered that there may be cases of combined infection—malaria with plague, and plague with relapsing fever. The writer was shown such cases in the Arthur Road Hospital in Bombay. In the same hospital, Khan Bahadur Dr. Choksey showed Dr. Flint and myself a form of plague in which there was an associated parotiditis, the plague bacillus probably entering the gland through the ductus parotideus. If there are venereal buboes, the size, resistance, and character of the tenderness of the enlargement will easily distinguish them from those met with in plague, and, further, in most instances, an initial venereal lesion will be discoverable. In all cases, including the various kinds of adenitis, the chief reliance must be placed upon the bacteriologic examination of the lymph glands and of the blood from the spleen.

An infection with anthrax might be confounded with the cutaneous form of the plague, but here, again, the bacteriologic examination, even of cover-slips, would suffice to differentiate the two diseases.

Plague pneumonia should not be confounded with croupous pneumonia. The sputum is decisive. It consists in plague pneumonia almost entirely of blood and plague bacilli. Microscopic examination of a cover-slip properly stained in carbol-thionin will reveal typical bipolar staining plague bacilli in enormous numbers. If the plague bacilli are few in number, or are mixed with other bacterial forms so that there is doubt with regard to its presence, a guinea-pig should be inoculated. It is emphasized by Childe that herpes is never present in a plague pneumonia.

If the first case seen is a septicemic case it is very likely to go unrecognized until after death. The hemorrhages and phenomena of general sepsis in the absence of apparent cause will then excite suspicion, and the bacteriologic examination will make the case clear. Nowadays, when cultures from the blood, *intra vitam*, are so often resorted to by clinicians for purposes of diagnosis in cases of general sepsis, we may hope for the discovery of plague septicemia even *in a first case* during life.

Dengue fever, prevalent in certain districts, might, on account of the general tenderness over the lymph glands, be confounded with

plague, but the characteristic exanthem and the mild course of the disease will usually permit one to recognize it even before a bacteriologic examination has been undertaken to establish the absence or presence of the plague bacilli.

It must be borne in mind that the peoples among which plague occurs in epidemics live under such conditions that careful clinical and pathologic examinations can be made only with considerable difficulty. Practice among the Chinese or among the Hindoos has, perforce, to be carried on in a much less satisfactory way than among Europeans or Americans. Where plague cases are actually known to be occurring in an Asiatic population the only safe method to pursue is to assume every case of fever among the living to be one of infection with plague until it is proven to be something else, and to regard every dead body as a plague cadaver until pathologic and bacteriologic examinations (including the inoculation of a susceptible animal) have demonstrated the absence of the plague bacillus.

TREATMENT. As to therapy there is but little to be said. The only remedy available in which any confidence is to be placed is the pest-serum of Yersin-Roux. The results obtained with Roux's serum at Oporto were very encouraging. Should the writer develop the disease he would wish to have this serum administered hypodermically in large quantities. Outside of the serum-therapy the treatment is wholly symptomatic.

As a prophylactic measure, Haffkine's inoculation is best for individual protection, though immunity for short periods appears to be afforded by injection of Roux's serum.

THE PATHOLOGY OF BUBONIC PLAGUE.

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My acquaintance with the bubonic plague dates from a visit to Hong Kong, made in the spring of the year 1899 while a member of the Commission sent by the Johns Hopkins University to study the diseases of the Philippine Islands. While engaged in out-fitting in Hong Kong opportunity was afforded the Commission, by the courtesy of Dr. Lowson, the civil physician in charge of the Kennedy-town isolation hospital and the mortuary, to inspect those ill of plague and to witness and conduct postmortem examinations upon those dead of the disease. During this period the several known varieties of the plague were observed. Bacteriologic examinations were conducted and a small collection of pathologic material made.

No especial use was made of the tissues collected in Hong Kong until recently, when, as a member of the National Commission[1] appointed to investigate the plague in San Francisco, another opportunity was obtained to study the disease and collect a supply of material. The study of this combined material, together with a record of observations upon the pathology of the disease as presented especially in San Francisco, will form the basis of the present paper.

The epidemic in San Francisco is not traceable directly in a continuous chain of instances to any previous epidemic. The first case discovered in San Francisco, in March, 1900, was accidentally met with, and could not be connected with any previous example or precise infected locality. And yet the fact that the victim was a Chinaman

[1] The Commission was authorized by the Secretary of the Treasury, and consisted of Professors L. F. Barker, F. G. Novy, and myself.

places, with great probability, the source of infection in the Chinese epidemic which has continued without interruption for the past six or seven years.

The Chinese of San Francisco, as of this country generally, are Cantonese, who embark at Hong Kong for America. Although no new importation of Chinese into the United States is known to be taking place at this time, yet the constant travel kept up by those who return for a period to China maintains a continuous communication between our western shores and the southern part of the Chinese Empire. The shipments of food-stuffs, wearing apparel, and objects of art from Hong Kong to America are constant, and constitute another bond of tangible connection between the two countries.

The first authentic account[1] of the appearance of plague in Europe is the great epidemic known as the Plague of Justinian, which in A.D. 542, starting from Egypt, spread to Europe and all over the Roman Empire, and which, lasting for fifty or sixty years, wrought the most frightful devastation. From that time until 1841, when the plague appeared for the last time in Constantinople, it recurred again and again in different parts of Europe, though latterly only in the southeastern parts of the Continent and in areas becoming gradually more circumscribed. In 1878 and 1879 a small epidemic, which speedily died out, broke out in the Russian province of Astrakan. With the latter exception and the recent limited epidemic in Oporto and Glasgow, Europe has long enjoyed exemption from the plague. America has never been visited until the recent appearance at Santos, Brazil, and the Argentine, and at San Francisco.

The mode of spread to America can best be followed by a consideration of the progress of the recent epidemics in Egypt, India, and China. Egypt, until 1899, had been exempt from plague since 1844, although several epidemics have since the latter date occurred in its neighborhood—in Tripoli (Benghasi), and on the Red Sea coast of Arabia (Assir), from 1853 to the present time. It is said to be endemic in Uganda and the *hinterland* of German East Africa (Koch). Many epidemics have occurred in Mesopotamia, Turkestan, India, China, and Mongolia.

In India there had been several outbreaks during the nineteenth

[1] This historic account is abridged and but little altered from the account of Manson, Tropical Diseases, 1901.

century, but they had been of a localized rather than of a general character. Probably plague is always present in some parts of India, epecially among the rude hill peoples. In 1896 it appeared in Bombay, and, possibly, in Calcutta, having been imported to the former city, most likely from Hong Kong.

It is now known that plague has been endemic in the southwest of China, in the province of Yunnan, for many years. It was particularly active from 1871 to 1873, after the great Mohammedan rebellion. From Yunnan, probably following the trade route, it spread to Pakhoi on the Gulf of Tonquin, a severe epidemic occurring in 1883 in that and in neighboring towns. In 1894 it had extended to Canton, where it killed, it is estimated, 60,000 in a population of 1,500,000 (?). Later in the spring of the same year it broke out in the English colony of Hong Kong, subsequently spreading to Macao, Swatow, Amoy, Foochow, Formosa, and probably many other places in the southern provinces of the Chinese Empire. Recently it has broken out in Mauritius, Madagascar, at Delagoa Bay and Cape Town in South Africa, Osaka, and Kobe, in Japan; Manilla, in the Philippine Islands; Hawaii, in the Sandwich Islands, and, lastly, as mentioned, at San Francisco, in the United States.

The evidence is complete and incontrovertible that the cause of plague is found in a specific bacillus discovered almost simultaneously by Kitasato and Yersin in the year 1894, during the prevalence of the epidemic in Hong Kong. The bacillus has a characteristic form; it exhibits a marked peculiarity in staining properties; admits easily of cultivation outside the body; readily and quickly undergoes involution upon artificial media, especially when concentrated so as to contain an increased quantity of salts (*e. g.*, sodium chlorid), and also in the tissues after degeneration and after removal from the body or death of the individual, if the examination be delayed for some hours, and is pathogenic for a wide range of animals, causing in them similar symptoms and lesions to those found in the natural infection in man and in the rat. As this paper does not pretend to deal with the purely bacteriologic aspect of the plague, a brief reference only will be made to the morphologic character of the bacillus.

As seen in recently affected and freshly removed tissues, in secretions or cultures, the bacillus of plague is a short rod, averaging 1.5 to 1.75μ in length and 0.5 to 0.7μ in width. The ends are rounded

and the sides convex, the form, therefore, approaching an oval. From the typical form there are two variations: one is shorter and coccoid, the other longer and more definitely rod form. A third variation is ovoid, in which one end appears slightly thicker than the other. All the forms tend to exhibit bipolar staining, the mid-portion remaining unstained or staining more lightly. Complete and uniform staining may, however, be observed. In older pathologic processes, and in older artificial cultivations, as well as upon concentrated media, various degenerative forms are found. These consist of oval, ovoid, almost circular, bladder-like, irregularly outlined and even bizarre bodies, which stain with difficulty, slightly, or even not at all, or stain at the margins and not in the interior. A not infrequent degenerative form resembles a dumb-bell or dough-nut (so-called "dough-nuts" of the San Francisco bacteriologists).

Staining is more readily effected in films than in tissues; but in both it proceeds relatively slow. Gram's method is negative. While all the common anilin stains can be employed for staining, the most useful results were obtained with carbol-thionin in weak solutions and after long immersion.

The present description is based upon the study of six cases of plague upon which postmortem examinations were made. Unfortunately, with one exception—Case VI.—complete autopsies could not be made.

The reasons for this deplorable fact will be found in the succeeding paragraphs, quoted from the official report of the Commission[1] appointed by the Secretary of the Treasury for the investigation of plague in San Francisco:

"In the study of the pathology of cases of plague met with among the Chinese in San Francisco a number of disadvantageous circumstances were contended with. In the first place, owing to the peculiar prejudices of this people—prejudices born especially of their religious beliefs and practices—permission for postmortem examinations is given with great reluctance. The opposition to all mutilation of the bodies of the dead is so great that consent for necropsies was obtained only after assurance that the examinations would be limited

[1] Report of the Commission appointed by the Secretary of the Treasury for the investigation of plague in San Francisco, under instructions from the Surgeon-General, Marine Hospital Service. Washington, 1901.

strictly to the actual necessities for the establishment of the diagnosis of the disease.

"In the next place, there is no public mortuary in San Francisco to which the dead bodies were or could be carried. Such examinations as were made were conducted in the narrow limits of a dimly lighted alcove in an undertaker's shop, or in the even worse habitations where the dead were found.

"Under the circumstances the postmortem examinations left something to be desired on the score of completeness, although in every instance the important question whether death was caused by plague was answered definitely."

The Postmortem Examinations.[1]

CASE I.—Chun Ah Chou, actor, aged forty-four years, died February 5th in Washington Street Theatre. Body well nourished, two or three dark-bluish spots on legs (possibly hemorrhages). On palpation of neck, axillæ, and groins some enlargement of the lymphatic glands of the groin was made out, though nothing corresponding to an outspoken bubo was visible. Incisions were made in each groin, extending from Poupart's ligament about one-third the length of the thigh. The tissues on the left side were swollen and edematous; the edema was serohemorrhagic in character, and the lymphatic glands were hemorrhagic and greatly swollen. On the right side the edema was less marked, and the glands, while distinctly enlarged and reddened, were less altered than those on the left side. Sections of the glands showed them to be uniformly hemorrhagic and swollen, and to contain frequent necroses visible to the naked eye.

The spleen was fully twice the normal size. It was softer than normal, the capsule was wrinkled, and the color deepened.

The examination of films from the glands, periglandular tissue, and spleen showed large numbers of bacilli decolorizing by Gram's method and presenting the morphology of B. pestis. Cultures and inoculations of guinea-pigs were also made.

CASE II.—Lum Hong Yuen, cook and waiter in the Chinese theatre. Illness of three weeks' duration. Said to have quit work on account of chancre and bubo three weeks before death. Four or five weeks prior to death he is said to have had a chill. On inspection of the body no evidence of a chancre could be found. In the inguino-femoral region a large mass of swollen, conglomerated lymphatic glands could be felt. Upon incision of the right groin from Poupart's ligament to the beginning of the middle third of the thigh serohemorrhagic periglandular edema and uniformly enlarged and reddened glands were found. The amount of fluid was considerable, although there was enlargement of all the glands; some of them reached to the size

[1] Free use has been made of the records of cases in the official report.

of a horse-chestnut. On section these were of a deep red color and soft consistence. Necroses were present.

The spleen was enlarged to fully double the normal size; it was softened and of a deep bluish-red color.

Films from the glands and spleen showed large numbers of bacilli having the morphology and staining properties of B. pestis. Cultures and animal inoculations were made.

CASE III.—Wong Chi Lui, cigarmaker, aged forty-five years. Illness of two weeks. Complained of fever, loss of appetite, and general uneasiness. There had been pain in the groin and lower abdomen, for which a Chinese doctor had applied a plaster of honey and salve. No history of venereal disease. For three or four days previous to death the man was unconscious. On inspection and palpation a large mass of swollen glands was discovered in the left inguino-femoral region. On incision enlarged glands were revealed about the saphenous opening and in the groin. The largest gland had the size of an English walnut, and was of a dark reddish-brown color; it was soft and juicy in consistence, and mottled with hemorrhages and with grayish-white patches of necroses. The less swollen glands were markedly injected and contained hemorrhages. The periglandular tissue was very edematous, fluid running freely from the incision.

The spleen was about twice the normal size, soft and friable.

Films from the glands and spleen showed bacilli presenting all the properties of B. testis. Cultures and animal inoculations as usual.

CASE IV.—Tom Shom, male, aged fifty-one years, actor in the Chinese theatre. Had been acting in the theatre two weeks before, although it had been stated that he had not been well for from six to seven months previously. On February 4th he became seriously ill with fever and delirium. There had been some vomiting. On clinical examination, February 8th (Dr. Barker), the patient was found lying upon his back in bed, with legs drawn up. He was in a state of semi-stupor; pulse 108, quick, rather full, but of low tension. The skin was hot and dry. Respiration 20 to the minute. The face had an anxious expression. There was no palpable enlargement of the glands of the neck and axillæ, but in the right groin several enlarged glands could be distinctly felt, and tenderness existed. Died on February 10th. Examination at necropsy showed a slight swelling in the right inguino-femoral region which, on incision, revealed slightly edematous subcutaneous tissue, with slight enlargement of the glands. The largest gland was the size of a filbert, and its surface was dark and hemorrhagic. On section it presented distinct hemorrhages. Other glands were swollen, soft, juicy, and hemorrhagic.

The spleen was enlarged, soft, and friable.

Films from the spleen and glands showed large numbers of bacilli having the characteristic properties of B. testis. Cultures and animal inoculations were made.

CASE V.—Foong Ah Fong, female, aged twelve years. No external signs of plague. The spleen only was examined (marked protest from child's rela-

tives). It was enlarged to about twice the normal size, and was diminished in consistence. Films showed a very small number of bacilli of the size of B. pestis, although the characteristic polar staining was not observed. Cultures were made, and a portion of the spleen was introduced subcutaneously into a guinea-pig, with positive results.

CASE VI.—Ung Ah Buck, aged forty-five years. The day before his death this man was seen alive and examined by Dr. Barker, who diagnosed the case, *intra vitam*, as one of cervical bubonic plague. The patient stated that he had been ill for two weeks. His neck had been swollen for one week, and the condition had been regarded as quinsy. The fauces were swollen and reddened, the swelling being very marked on the left side. The left palatine tonsil was much enlarged, and showing on its surface a grayish-white patch the size of a dime. The reddening of the throat was general, and there was less local injection than one ordinarily sees in diphtheria. On inspection and palpation of the left side of the neck marked bulging was found, due, it seemed, to enlargement of the cervical lymphatic glands. Autopsy: the left side of the face and neck presented a marked diffuse swelling, extending from the angle of the jaw backward to the sternocleidomastoid muscle, and below almost reaching the clavicle.

On incising this region the parotid gland was first reached; this organ presented a normal appearance. After dissecting away the parotid gland a group of greatly enlarged, deep glands, surrounding the carotid artery and jugular vein, came in view. The periglandular tissues were infiltrated with bloody fluid and presented a sodden appearance. The enlarged glands and portions of the surrounding tissue were excised; the former were found to be swollen (several reaching the size of an English walnut) and to be wholly altered in appearance and consistence. In color they were deep purplish, and on incision a hemorrhagic fluid exuded. Opaque points of necrosis were also present.

The general subcutaneous fat was well developed; there was no general edema. The peritoneum appeared smooth and glistening; there was no fluid in the abdominal cavity, and the abdominal glands were not markedly swollen.

The spleen was enlarged to fully twice its normal size; it presented a purplish color and its consistence was diminished.

The pleural cavities were dry; the lungs retracted moderately upon removal of the sternum; the lower lobes were congested, but no consolidation was made out.

Films, cultures, and animal inoculations were made from the organs and tissues removed at this necropsy, consisting of the enlarged cervical glands and spleen. Cover-slips from the spleen showed large numbers of bacilli having the morphology and staining properties of the B. pestis. The films from the glands differed in their appearance. In some instances there were present large numbers of bacilli similar to those in the spleen, together with a few diplococci or short chains of cocci. Other cover-slips showed, beside the organisms mentioned, a bacillus having the morphology of the B. diphtheriæ.

The Histologic Examination. The description of the microscopic appearances is based upon the study of the material collected in Hong Kong in 1899 and in San Francisco in 1901. The sections were prepared by Dr. Pearce, to whom my thanks are due. The material covers especially the bubonic cases, hence the descriptions will refer almost exclusively to the changes in the lymph glands and spleen. Tissues from two cases of tonsillar infection (one from Hong Kong) are also available for study. The animal tissues cover a wide range, and include all the organs except the central nervous system. They were obtained from guinea-pigs inoculated with bits of tissues and cultures in San Francisco, and represent the different experimental effects produced by the plague bacilli. Some of the animals succumbed quickly to septicemic infection, others after many days, in which case pronounced local (bubonic) and visceral lesions were noted; in a few instances the animals were etherized in order to establish the diagnosis or to obtain intermediate effects.

Human Cases. As no histories were obtainable of the cases from which tissues were collected in Hong Kong, and none that were reliable from those in San Francisco, no attempt will be made to consider the disease with respect to its duration; but the degrees of severity of lesions will be described as exhibited by the grade of involvement of the organs studied. The chief distinctions will be afforded by the lymphatic glands, and they will depend upon whether the glands were primarily or secondarily affected. Primary involvement may be of two kinds: Of the first order, being the point of original reception of the virus; of the second order, representing the extension to a second contiguous group of glands. As might be anticipated, buboes of the second order are less marked than those of the first order. Secondary buboes may be found in any or all glands within the body, and at a distance from the primary lesions, infection having followed through the blood circulation. They present, as a rule, an example of involvement of least intensity.

Lymphatic Glands—Primary Buboes of Second Order. These glands show to the naked eye slight swelling and congestion. Upon microscopic examination, in the least marked cases, the changes affect especially the lymph sinuses. As might be anticipated, the subscapular sinuses show very early involvement. Even when the medullary ones show very slight alterations the cortical sinus is dilated and contains numerous large cells, with round

nuclei and finely granular and vacuolated protoplasm. These large cells quite completely fill the sinus. When the subscapular space exhibits this condition, and it is present in glands that are regarded as scarcely enlarged, similar cells are to be found about the main trabeculæ in the interior (medulla) of the gland. That they are the cells that later show marked phagocytic properties for red blood-corpuscles is certain. In this early stage the lymph nodes and cords are little affected. There may be some increase in the lymphoid cells about the larger veins, but no very marked alterations have, as yet, taken place. There is complete absence of necrosis. Throughout the gland fine strands of fibrin can be seen, indicating doubtless an inflammatory (?) edema. The bloodvessels contain light, fibrinous, possibly agonal or postmortem thrombi. At a later stage, when the glands are definitely although not greatly enlarged, the changes are more diffuse and more profound. All the sinuses are much enlarged; the cellular proliferation within them is also a marked feature, and the new cells are highly phagocytic exclusively for red blood-corpuscles. These cells cannot be distinguished from the red blood-corpuscles carrying cells of the spleen in typhoid fever. The lymphoid cells proper are also increased, beside which the centers of the lymph nodes and cords show a great increase in swollen and pale cells, their centers being converted into pale areas composed of cells of the epithelioid type. A small number of nuclear fragments also occur in these areas and chiefly within cellular protoplasm. The foci described are similar to those found in lymph glands and the spleen in other infectious or toxic diseases—*e. g.*, diphtheria and typhoid fever.

The bloodvessels in the early stages of swelling contain an increased number of mononuclear and polymorphonuclear white cells. As the intensity of the process grows their number increases. With the progress of the swelling, etc., the number of vascular thrombi increases and their nature changes. They appear in large vessels and contain many more white cells.

The relation of plague bacillus to these buboes is perhaps variable. What I should take to be the normal is a small growth, especially in the blood and lymph vessels, the bacilli demonstrable among the lymphoid cells being fewer. The bacilli exist free among blood-corpuscles and other cells. On the other hand, I have seen in buboes of the second order a growth of bacilli as great as in those of the first order. What is, however, very striking in these instances is the absence of anything like an adequate reaction on the part of the gland; and, moreover, the existence with as little reaction of equally large masses of characteristic bacilli in the periglandular adipose and other tissues. I am, therefore, inclined to view this abundant growth either as being agonal, or, what I think even more probable, as of postmortem development.

Primary Buboes of the First Order. The pathologic changes in these glands are unmistakable. They exceed in intensity and in extent those of the preceding order. They, moreover, differ in kind, first, on account of the occurrence of hemorrhage, and, second, on account of the necrosis. The two sets of lesions can be compared with difficulty on account of the degree to which

the structure is lost by necrosis, etc., in the glands now being considered. Again, while the periglandular affection in the former order was slight, the outline of each gland being defined by its capsule, in the present one such sharp limits are entirely missing; the periglandular involvement is as great as the glandular affection, and the necrosis, hemorrhage, etc., are as marked. On account of the nature of the interglandular tissue, the presence of large blood and lymph vessels, nerves, etc., the histologic appearances differ from those of the glands themselves.

In all the specimens of glands which I have examined no separation into the medulla and cortex is possible. Masses of lymphoid cells still remain, but they do not compose typical structures. That they are the relics of cortical structures their position proves; but they are not in relation with a definite systematic arrangement. The medulla is even more altered in that all the proper cells are necrotic. Only fragments remain of the large, swollen, phagocytic cells, and the intercellular stroma stains poorly or not at all. What can be made out clearly are granular material, containing remains of cell-forms, nuclear fragments in small numbers, shadows of red corpuscles, and plugs of finely granular structures, filling spaces which suggest pre-formed vessels, and which, from the regularity of the grains, can be recognized in the hematoxylin specimens to be bacilli. This granular and amorphous detritus is continuous with similar material in the cortex, only that in the latter situation small foci and islands of lymph cells still persist. This same regular, granular appearance mentioned proves that many bacilli occur throughout this entire area. Hemorrhages also exist in the cortical parts.

The bloodvessels commonly are thrombosed. The thrombi consist of cells, both mononuclear and polymorphonuclear, and fibrin. The walls of the smaller vessels often are hyaline and structureless. Specimens stained with the fibrin stain show a fine network about the vascular walls, occurring partly within the lumen, partly within the wall, and partly beyond the perivascular tissues. Larger vessels show, instead of the fibrinoid transformation of their walls, destructive and infiltrated changes. The intimal and medial coats contain an increase of cells and many cell fragments. This infiltrative condition is especially marked in the middle coat. That many of these cells are polymorphonuclear blood cells is shown by the bizarre forms, etc., and the staining properties.

The periglandular structures are extensively infiltrated and usually show necrosis as well. The infiltration is partly cellular, partly fluid, along with which fibrin is perhaps invariably present. The cells consist of red corpuscles and small elements with single, deeply-staining, much fragmented, or polyform nuclei. The edema and fibrin are found chiefly in the coarse, fibrous septa of the adipose tissue; the cells occupy the meshes of the fat cells. The necrosis may be microscopic in extent, affecting a small number of cells, or large areas may be without definite structure and present a granular appearance. The bloodvessels are frequently thrombosed, and their walls inflamed (as above).

The nerves are involved in the exudation. The cellular infiltration is

found only in the perineurium, but this may be invaded to such an extent as to present the appearances of a small-celled collar surrounding the nerve bundles. The bloodvessels within the nerves are dilated; the nerves (in alcohol preparation) appear swollen, and the cells of the endoneurium are occasionally fragmented. Vessels with thin walls, presumably lymphatics, contain formless plugs in which there are many bodies taken to be bacilli.

Bacilli are abundant within the swollen glands and in the periglandular tissues. Sections stained in thionin show countless numbers. In no known bacterial infectious process, not even in leprosy, are such large numbers of bacteria to be found. They occur in continuous growth throughout the glands, occupying every available space; they completely occlude many bloodvessels, or, mixed with definite thrombi, compose a considerable part of the plugs. Moreover, the walls of the bloodvessels contain masses of bacilli, having grown, it is safe to conclude, within the vasa vasorum and the lymph spaces. The adventitial coats of veins and arteries are especially rich in such growths of bacilli. The bloodvessels and lymph vessels of the periglandular structures are also, to a large extent, occupied by bacilli. The latter seemed to be plugged by these growths alone; the former may show bacterial masses, even when the vessel is still open and pervious. Large areas of finely granular detritus in the interstitial tissue are made up of a massive growth of bacilli; and the bacilli occur in the fluid exudate. The morphology of the organisms speaks unmistakably for the bacillus pestis.

The Tonsillar Infections. The buccal mucous membrane forms one of the portals of entry into the body of the plague bacilli. It is probable that the cervical buboes arise from that source of infection. Of all the buccal structures the tonsils seem to be most frequently the primary one attacked. In this fact we have only another illustration of the importance of incomplete epithelial investment and perhaps of previous disease in promoting infection. Other parts of the buccal cavity may become secondary points of development of the bacilli, an example of which is supplied by a case from which tissue was obtained in Hong Kong, and which shows early involvement of the epiglottis.

The tonsil suffers changes not unlike those described in the primary lymphatic bubo of the first order. There is congestion, hemorrhage, necrosis of cells, and extensive growth of bacilli. The degrees vary somewhat, so that examples of lymph sinus proliferation may be met with along with other changes of greater severity. The cells of the sinuses are somewhat smaller than in the lymphatic buboes; some resemble Unna's plasma cells closely, *and many are phagocytic for bacilli.* Of this there can be no doubt, for the protoplasm of these cells is packed with characteristic organisms. The bacilli are spread beneath the layer of stratified epithelium, even elevating this layer through the excessive growth, the epithelium showing vacuolation, loss of nuclei, etc.

The lesion of the mucous membrane covering the epiglottis is more recent than in the tonsil. It consists of a marked infiltration of small cells with single nuclei, polymorphonuclear cells, and serum. The infiltration extends

to the layer of mucous glands next the cartilage, which are in part broken up by it. The chief growth of bacilli is near the surface, beneath the epithelium, which layer, it should be mentioned, is in part deficient. Occasional masses of bacilli occur in the deeper layers and even within the lumen of the glands. The appearances here presented are not unlike those described of the primary plague pustule.

The adjacent glands suffer along with the tonsils; their enlargement constitutes, of course, the cervical bubo. Two kinds of glands must, however, be distinguished in this region—lymphatic and hemolymphatic glands. The former undergo the changes already described. In addition, it should be mentioned that even with considerable enlargement the alterations noted in one gland—the one constituting the main bubo—resemble closely those of the glands of the second order, except for greater richness in bacilli pestis. The lymph sinuses especially were affected; the cells were increased in numbers, enlarged, plasma-cell forms occurred, but phagocytosis was for bacilli only. The lymph node and cord cells were also increased, but not degenerated. Occasional mitoses were met with in larger (endothelial) cells.

The *hemolymph* glands were greatly enlarged; the network of vessels enormously distended; much hemorrhage had taken place; nuclear fragments were scattered numerously throughout the tissue; a small number only of cells with undegenerated nuclei were still present; the periglandular tissue was hemorrhagic, and micro-organisms—bacilli—were abundantly present. In Case VI. of the San Francisco series the very hemorrhagic glands described consisted of these structures.

The Spleen. As already described, the spleen in the plague is enlarged moderately; the consistence is somewhat diminished, and the color deeper than normal, but it is not the type of the acute splenic tumor of the true septicemias. In making this statement it is well to emphasize that although the spleen in the autopsies made all contained bacilli, often in very large numbers, the cases themselves were examples of the bubonic and not of the septicemic variety, *per se*, of the disease. In a case of pneumonic plague which I saw with Lowson at Hong Kong the spleen was much swollen (three to four times the normal size), and very soft and dark.

It is probable that, irrespective of their mode of origin, all fatal cases of the plague are septicemic (bacteriemias). But it is also probable that the general invasion of the bacilli takes place late in many bubonic examples, and the enlargement of the spleen is, therefore, less marked a feature than in the primary septicemias, or even the pneumonic variety in which dissemination of the organisms occurs earlier in the course of the disease.

The microscopic changes vary in different cases, but in degree *only*, so far as can be determined by the study of bubonic cases. The alterations affect the pulp chiefly, next the lymph nodes (Malpighian bodies), and then the bloodvessels and stroma.

The pulp is swollen, the swelling being the result of cellular proliferation, cellular infiltration, and edema. The proliferation affects especially cells closely united with the veins and surrounding the trabeculæ. These cells

have reticulated nuclei, placed eccentrically, and a fair allotment of protoplasm taking the blue thionin stain. The cells are often polyhedrical rather than round. These cells have a close affinity to Unna's plasma cells. Next the lymphoid cells are increased, but to a less extent than the cells just described. The vascular and other (?) spaces in the pulp contain an increased number of red corpuscles. In the same spaces occur large cells of two kinds. One is a giant cell with single, lightly staining, reticulated nucleus and a moderate amount of protoplasm, and resembling the large, mononuclear, narrow cell with which it is probably identical; it is not phagocytic. The other is a much larger cell, three to four times as large as the narrow cell, and is highly phagocytic. These macrophages englobe white cells—both mononuclear and polymorphonuclear—but rarely red corpuscles. They occur at times within the larger veins, especially such as exhibit the subintimal cellular proliferation to be described. The polymorphonuclear cells in the pulp exhibit great variation in form, and many would seem to have been in a state of active migration when the tissue was fixed. They show great variety of form, such as is seen in actively motile cells, and they would seem to be moving in numbers through the pulp. Fibrin, in the form of balls and fine strands, is found among the pulp cells and in the fluid, and many bacilli are present.

The Malpighian bodies are increased in size, the increase being due to the multiplication of the lymphoid cells, and, to a smaller extent, of epithelioid cells. The latter do not occupy the centers of the nodes, but are few in number and placed peripherally. Their nuclei are large and vesicular; rarely a cell contains two nuclei. Degeneration of cells is uncommon, very few fragmented ones being visible. Rarely small islands of fibrin are present in the nodules.

The bloodvessels show two kinds of change. The arteries, chiefly those of the Malpighian bodies, have hyaline walls; the veins of all sizes frequently show subintimal cellular proliferation. The cells in the intima are mononuclear and more rarely polymorphonuclear elements that form a continuous although not uniform investment, or appear as isolated projections into the lumen of the vessel. Above these cells the displaced endothelial cells can usually be detected.[1]

Bacilli are very numerous, especially in the pulp, where they grow diffusely and would seem to attach themselves to the reticulum and grow in irregular masses into the venous sinuses. They are rarely within cells. Their morphology is unmistakably that of B. pestis. They also completely occlude small bloodvessels, and, within the trabeculæ spaces, probably lymphatics. In that the richest growths are often unassociated with reactions, it is highly probable that they may have taken place postmortem.

So few specimens of the remaining organs could be collected that no description of them will be attempted.

[1] This process is identical with that described by Hektoen in tubercular meningitis; Councilman in epidemic cerebrospinal meningitis; Pearce in the spleen in scarlet fever, and Flexner in the lung in experimental leptothrix filiformic pneumonia in the rabbit.

The Experimental Disease—Morbid Anatomy. As stated at the outset, the animal used for experiment was the guinea-pig. The inoculated material consisted of bits of spleen and lymph gland and cultures upon agar from those sources. The place of inoculation was the subcutaneous tissue of the lateral abdominal wall, nearer the inguinal than the axillary region.

The inoculated animals[1] can be separated into two groups, depending upon the results of the inoculation. These results in turn depended upon the virulence of the material—tissue or culture—inoculated, upon which also depended the duration of life following inoculation.

Types of Infection. The animals inoculated early in the course of the investigations in San Francisco died at periods varying from forty hours to eight days. Those inoculated later, and one or two inoculated with cultures early in the studies, but which had not succumbed, were etherized at the close of the work and subjected to postmortem examination. According to the period of survival and virulence of the inoculated material, the appearances observed denoted (*a*) bacteriemia without microscopic localization in the organs, and (*b*) focal, nodular localization in the internal organs. In all cases marked local lesions at the site of inoculation and in the adjoining tissues occurred.

Local Lesions. At the point of inoculation the tissues—skin, subcutaneum and sometimes muscles—were infiltrated with pus cells and presented a yellowish focus of necrosis. From this area as a center the subcutaneous tissue, sometimes of one side, but frequently of both sides, was occupied by gelatinous, hemorrhagic infiltration.

The lymphatic glands of the inguinal and axillary regions, even in the acute cases, were distinctly enlarged. In those animals which died after a longer period, or were killed from six to seven days after inoculation, the regional lymphatic glands were much enlarged, hemorrhagic, and even necrotic. The inguinal glands were, as a rule, more swollen than the axillary.

The Spleen and Liver. In the instances of rapid death (bacteriemia) the spleen was moderately enlarged, its color was deepened, its consistence decreased, but no focal lesions were visible to the naked eye. In this class of cases the other organs failed to show focal lesions. The lungs appeared mottled only, and a few small necroses existed in the liver; numbers of bacilli were contained in all the viscera and in the heart's blood.

The focal lesions in the spleen consist of grayish-white nodules, larger than a millet-seed in size, covering the surface (within the capsule), and occupying the substance of the organ. When the nodules are numerous, as—*e. g.*, in animals succumbing from the sixth to the eighth day, or after etherization at that period, when there has been a marked local reaction—the spleen is greatly enlarged, perhaps five to six times its normal size, and its color is pale. The main mass is composed of the nodules now almost or actually con-

[1] See Report of the Commission, p. 17 et seq.

fluent which, having penetrated the peritoneal capsule, are covered on the surface with a fibrinous exudation.

The liver invariably shows lesions when death has been delayed a few days. The common ones are focal necroses of varying size. These are yellow in color, and in size ranged from that of a pin's point to linear and wedge-shaped areas three to four millimeters in length. Only rarely did whitish nodules similar to but smaller than those noted in the spleen occur.

The Lungs. They present a variety of appearances, only one of which was characteristic. Sometimes they showed no gross lesions; not uncommonly they are mottled and contain small ecchymoses beneath the pleura; rarely they contain scattered whitish nodules resembling those of the spleen, except that they are smaller and tend to be surrounded by a zone of recent hemorrhage. No effusion into the pleura was noted.

Subserous Hemorrhages, These are common, especially in the peritoneum, where they occur beneath and within the serosa of the large intestines; and in the pleura covering the lungs. They are usually small in size, although at times, through confluence, they reach larger dimensions. However, considerable exudations or effusions into the serous cavities did not arise from this source.

The other organs, except the adrenal glands, showed no special changes to the naked eye. The adrenals were uniformly congested, and often very dark in color.

The central nervous system was not examined.

Histologic Examination[1]*—Local Lesions.* This embraces (1) the site of inoculation, and (2) the adjacent lymphatic glands. 1. Upon microscopic examination it is found that the abdominal muscles are involved in the local infection. The lesion consists of necrosis, extensive infiltration, and proliferation of the local tissues. The infiltration exceeds the necrosis, but the proliferative changes are considerable. The necrotic tissue is infiltrated with cells containing polyform and fragmented nuclei, many staining very poorly. Among these a fair number of cells with single vesicular nuclei are also found, they probably arising from the fixed tissues. The cellular and necrotic mass is surrounded by voluntary muscle, fibrous, and adipose tissue. Remains of these several tissues may also be found in the phlegmon, especially fragments of muscle; but the adjacent muscle fibres are swollen, sometimes fragmented, and if the phlegmon is large much compressed and elongated. But the main change is found in connection with the sarcolemma, which is in active proliferation, separating widely the remaining fibers in the older specimens, and giving rise to a marked interstitial myositis. The adipose and connective tissues are also in active proliferation. Newly-formed blood-vessels are numerous, and the phlegmon is enclosed by the new tissue.

Notwithstanding the evidences of healing and the marked reaction, the

[1] The histology of experimental plague lesions has received relatively little attention. The main description, with the facts of which the above is in considerable agreement, is given by Babes and Levaditi, in Virchow's Archiv, Bd. cl., 1897, p. 343.

number of bacilli present is very great. They appear in large clumps and in the form of a diffuse growth, not only in the phlegmon, but also in the adjacent newly-formed tissue, and are largely without cells.

2. The lymphatic glands show degrees of swelling, etc., in part according to their positions, and depending upon their mode of infection. Division into primary buboes of the first and second order is also justifiable in animals. The main lesions consist of hyperemia, cellular proliferation, exudation, and bacterial growth. The cellular proliferation and bacterial development predominate. The former is met with in the medulla and the cortex, and affects lymphoid cells (in the cortex especially), and a larger cell with eccentric nucleus and more abundant, deeply-staining protoplasm (chiefly in the medulla). The larger glands (primary buboes of first order) show much necrosis, the cells being extensively fragmented. In these, moreover, fibrin is present, both as fine fibrils throughout the gland and in the form of more compact masses within the vessels. As many of the plugged vessels are in the medulla, occupy the position of the lymph sinuses, and are devoid of red corpuscles, they are taken to be lymphatic vessels.

The periglandular tissues are invaded also. Infiltrations, exudations, and necroses are met with in the cellular and adipose tissue; bacteria are also numerous. The bacilli in the main buboes are as numerous as in cases of human infection, and have much the same distribution. An exception is found in the less conspicuous involvement of bloodvessels in the experimental buboes.

The Spleen. There is little similarity in this organ in the human and experimental disease. The sole diffuse change in the latter is congestion, which is often so marked a feature as to cause wide dilatation and make very conspicuous the blood sinuses of the pulp. The white cells also are increased, and especially a large mononuclear cell. The Malpighian bodies are but little altered. Unless there have been nodular formulation in the spleen little else is found except bacilli, which may be abundant, especially in the pulp.

The localized nodules are what constitute the characteristic lesion. They consist of a central body of bacilli about which are grouped cells and remains of cells, forming collections as large as or larger than the Malpighian bodies. The bacilli may form a central mass with radii projecting from the periphery, or the development may have taken place from several centers, the latter being united by intervening strands. The cells surrounding the bacilli are in part mononuclear elements, having vesicular nuclei; but in the main they are polymorphonuclear, fragmented, and degenerated cells. In one specimen, areas composed only of mononuclear cells, but with slight bacterial development only, were observed. Fibrin is present about the areas, within the vessels, and in the tissues. The quantity of fibrin varies in the different specimens.

From the position of the bacilli it would appear that they developed in bloodvessels, which finally became occluded. Following this cellular proliferation doubtless took place, although previous degeneration of splenic

tissue may have occurred. The degeneration of the new cells seems to have provoked a rich emigration of leukocytes toward the areas of bacterial development. The bacteria are free, without cells. In addition to the masses (emboli?) of bacilli a general diffuse growth of organisms is also present in the splenic tissue.

The Liver. The focal lesions of this organ consist, beside rare hemorrhages, of necroses and nodular formations not unlike those found in the spleen. Of the hemorrhages, which do not reach a large size, it is unnecessary to speak further; the necroses are, however, important. The latter are separable into two groups: those attended and those unattended by proliferative phenomena. Together they constitute the necroses described as visible on the surface of the organ as dots and lines. Similar ones may be present also in the depth, and in both the liver cells are found in various stages of hyaline or coagulative necrosis. The protoplasm is highly refractive, shows an increased affinity for eosin, the nuclei of the cells may be absent, in a state of pyknosis, or fragmented. Remains of previous vacuolization or fatty change may be discovered in the dead liver cells. A small number of leucocytes may occupy the capillaries between the cells. Bacilli are sometimes demonstrable in the sections among the hyaline cells, sometimes not. They doubtless are always present, but not clearly stainable. Thrombi are usually absent.

A more characteristic lesion is found in the nodules with which necroses of liver cells are usually associated. The nodules vary in number, position, and size in different specimens. In some instances they were entirely absent, although the simple necroses existed. They are associated, perhaps invariably, with considerable growths of bacilli, forming zooglea masses, which occupy the centers of the nodules. About these there is a rich cellular accumulation, which I take from the study of many sections to arise as follows: The bacilli having localized within the liver, a multiplication of the endothelial cells of the neighboring capillaries takes place. As these cells—presenting epithelioid appearances—increase the adjacent liver cells also begin to show alterations, among which are swelling and vacuolization of protoplasm, multiplication of nuclei, compression of protoplasm, and hyaline degeneration. A little later stage exhibits the disappearance of many of the liver cells, their place having been occupied by the epithelioid cells, so that the new formations at this time look not unlike miliary tubercles. One difference is, of course, immediately noticeable, the bacilli being numerous and easily demonstrable. Another difference is found in the tendency of the node to enlarge by exciting the adjacent structures to similar proliferative activity. Finally the large size of the nodules and the extent and irregular distribution of the liver necroses constitute marked differences from the appearances seen in tuberculosis. Moreover, there is no caseation in the nodules, or any process to be confounded with it, although disintegration by fragmentation of cells commences very soon. About this time polyform cells, probably polymorphonuclear leukocytes, make their appearance and mingle with the other cells. In the oldest nodules nothing remains of unaltered or only slightly changed liver cells in the centers of the formation.

The nodules may occur anywhere within the liver lobule and in the interlobular tissues. Thrombi, hyaline and fibrinous, may be present in the adjacent veins and capillaries. The cellular proliferation and infiltration, instead of giving rise to a definite node, may extend in a linear direction along the walls of bloodvessels or bile vessels. In the former the endothelial lining of the vessels tends to increase. In one specimen a considerable linear envelopment was noticed along one side of a medium-sized branch of the hepatic vein.

The effects of the presence of the bacillus pestis in the liver of guinea-pigs is to cause general and local degeneration, and, by their occurrence in large numbers, to excite circumscribed proliferation of the endothelial cells and perhaps, although only to degenerate quickly, the liver cells. The lesion which results from the latter process is the characteristic plague lesion in the liver, and corresponds more or less accurately with the focal lesions in the spleen. It is the result of the direct action of the bacilli or their metabolic products *in situ*. The more remote effects of the bacilli are degenerative only.

The Lungs. Subpleural and intrapulmonary ecchymoses are not uncommon. The characteristic lesion is, however, focal and nodular. In number, size, and distribution these nodules are subject to great variation. They may be absent altogether, very few may be present, or every section of the lungs may contain a dozen or more. They may be near or within the pleura, in the substance of the lungs, or adjacent to bronchi. In size they vary from the area of two or three to areas of twelve or more pulmonary alveoli. Bacilli in masses are always present. They are within the alveolar spaces and in the pulmonary capillaries. About these are cells, the major being within the alveoli, and consisting of or resembling the alveolar epithelium. Cells with polyform nuclei and cell fragments are intermingled. The stroma is also infiltrated with similar cells. The larger the nodules the more irregular in form the cells, and the greater the number of fragments. Beside the bacilli within the nodules a growth may also have taken place in the pulmonary capillaries, about which there may have been no considerable cellular accumulation.

The adrenal gland shows extensive hemorrhage, marked especially within the medulla, the structure of which is greatly disturbed. The cortex, on the other hand, exhibits an extensive growth of bacilli, which occur between and surround the cortical cells and occupy spaces beneath the capsule of the gland. Isolated masses of bacilli are also present in the medulla.

The present epidemic of plague in China and India has been noteworthy, first, because of the discovery of the specific cause, and, second, as permitting accurate studies of the varieties, modes of infection, prophylaxis and specific treatment of the disease. A host of contributions to our knowledge of the plague have been made by private individuals and Commissions sent to the East by Japan and

several European countries. Brief reference will be made in this place to the pathology of the disease, as described in some of the published reports, in order that comparison may be made with the San Francisco epidemic, which supplied the chief materials for the present paper.

According to the German Commission,[1] the pest bacilli find their way into the body either through wounds of the skin or by way of the lungs. The first mode of infection gives rise to the great majority of the cases. It is presumed that minute lesions—scratch wounds, etc. —open the way. No unmistakable example of intestinal infection was observed, while, on the other hand, instances of infection starting from the tonsil or other parts of the buccal mucous membrane were encountered. In a considerable proportion of cases pustules or carbuncles of the skin, representing the primary points of entrance, from which the regional lymph glands became affected with bacilli, were noted, and between the two stations distinct lymphangitis is said to have occurred. Bubonic plague may eventuate in absorption, in suppuration, or it may be associated with severe symptoms, denoting spread of the infection or a general intoxication of the organism. The hemorrhages which are present in various parts are due to intoxication, in support of which conclusion an instance of the examination of a fetus expelled on the third day of the disease is cited. In it typical hemorrhages were present, but no bacilli whatever could be demonstrated in cultures, etc. Bacilli were not, moreover, obtainable from petechial blood. The commission also recognized a severe form of the plague—the pest septicemia—and in addition a primary plague pneumonia that may be mistaken for croupous pneumonia.

The report of the Austrian Commission[2] differs in some respects from the German, and it is important as containing extensive descriptions of the gross and microscopic appearances of the organs in the plague.

[1] Mittheilungen der Deutschen Pest-commission aus Bombay, etc., Deutsch med. Wochenschr. Sonderbeilage zu No. 17, 1897; Weitere Mittheilungen der Deutschen Pest-commission, ibid., Nos. 19, 31, 32, 1897; Gaffky, R. Pfeiffer, Sticker und Dieudonné: Bericht über die Thätigkeit der zur Erforschung der Pest in Jahre 1897 nach Indien enstandten Commission, Arbeiten a. d. Kaiserl. Gesundheitsamte, Bd. xvi., 1899.

[2] Zusammenfassender Bericht über die Thätigkeit der von der Kaiserlichen Akademie der Wissenschaften in Wien zum Studium der Pest nach Bombay entsendeten Commission (Wiener klin. Wochenschr., No. 20, 1897; Müller, Albrecht und Ghon, Ueber die Buelenpest in Bombay in Jahre 1897. Gesammtbericht der von der Kaiserl. Akademie der Wissenschaften in Wien zum Studium der Buelenpest nach Indien entsendeten Commission. Theil 1 and 2, A und B, Wien, 1898-99).

The report was based upon the clinical observation of seventy cases of plague and the bacteriologic and pathologic examination of forty-seven cases. The chief form of plague is denominated by them "septicemic hemorrhagic." It is characterized by a primary hemorrhagic bubo located most frequently in the inguinal, axillary, and cervical regions, about which there occurs a hemorrhagic edema, and at a greater distance hemorrhages into the organs. The spleen is swollen, the general lymph glands are enlarged, and the parenchymatous organs show degenerative changes. The primary bubo may be entirely wanting, the swelling of the lymph glands may be inconspicuous, and the hemorrhage may be the only pronounced sign. A second form of the pest is the septicopyemic. In it embolic foci are present in the lungs, liver, and kidneys. A third form is the primary pest pneumonia, which is a confluent lobular pneumonic process, usually unattended with noticeable lymphatic enlargement. The common place of entry of the bacilli is the skin, but only exceptionally can the precise point of entrance be discovered, the demonstration of the place and mode being found in the location of the primary bubo. The lymphangitis in the neighborhood of the buboes as well as the infiltration of the periglandular tissue are always secondary to the glandular infection. A tonsillar infection is described, and the lungs are admitted to act as the portal of entry for the bacilli in a small number of cases. A single instance of purulent meningitis, due to the bacillus pestis, was encountered. Clinically, there should be distinguished only bubonic and pneumonic forms of the plague. The former is much the more frequent. In all but a very small number of cases the primary morbid focus is found in a lymph gland or a group of glands (primary bubo) from which, through lymphatic communication, the adjacent glands become infected. The latter constitute the primary bubo of the second order, in contradistinction to secondary buboes, the result of general invasion of the body by the bacilli. The invasion of the blood takes place always from the primary bubo (or lung), as a primary blood infection does not exist. The primary bubo may be so small that it cannot be discovered clinically, and is found anatomically only after careful and prolonged search. In *foudroyante* cases it may fail altogether.

The primary bubo is distinguished by destruction of the lymphatic parenchyma, necroses, hemorrhages, and (in the cases of mixed pyo-

genic infections) suppuration. A similar condition is found in the surrounding cellular tissues. Bacilli are present in colossal numbers. The secondary buboes show, on the other hand, uniform hyperemia, occasional hemorrhages, and, in the more protracted cases, medullary swelling. The primary buboes of the second order approach one or the other of these appearances, depending upon their distance from the gland primarily affected.

The multiple hemorrhages are not the results of the action of toxins elaborated at a distance, but are caused directly by the bacilli which may always be found in the neighborhood.

Parenchymatous and fatty degenerations of the heart, liver, and kidneys occur commonly. Splenic tumor is a constant occurrence. The spleen shows marked changes. The pulp is distended with blood, and contains many polymorphonuclear cells. The follicles are but little altered, but the trabeculæ are swollen and homogeneous. In some instances the endothelial cells of the pulp have proliferated and desquamated. When very great numbers of bacilli are present miliary necroses may occur (also observed by Yamagiwa).[1] The bacilli may be very abundant in the pulp, but are spare in the follicles. They are sometimes contained within cells.

In the pyemic variety metastatic foci are found in the liver, lungs, kidney, spleen, and musculature. These foci, which may reach a hazel-nut in size, resemble abscesses, except that they tend to be surrounded by a zone of hemorrhage. In about one-third of all the cases of plague secondary pyococcal infection has taken place.

The primary plague pneumonia appears in the form of a lobular consolidation, which, when the foci are numerous and confluent, may produce lobar solidification. Bronchitis is present. The bronchial lymphatic glands present appearances of primary, the other glands of secondary buboes. In addition to the primary two other forms of pest pneumonia are recognized; one metastatic, which appears as multiple and larger foci, seated beneath the pleura; the other an aspiration pneumonia, from inspirations of infected material obtained from buccal buboes.

Wyssokowitz and Zaboltney,[2] who were sent by the Russian Government to Bombay, performed autopsies upon twenty-four plague

[1] Ueber die Bubonen-pest, Virchow's Archiv, 1897, Bd. clix., supplement.
[2] Recherches sur la peste bubonique, Annales de l'Inst. Pasteur, 1897, t. xi., No. 8.

cadavers. They recognized two modes of infection—from wounds and through the lungs. In the former cases lymphangitis was usually missed, so that the exact place of entrance could not always be given; on the other hand, the territory of infection could be determined by consideration of the glands primarily involved. In their series of pneumonic cases (six) all were examples of bronchopneumonia. In no instance was a gastrointestinal source of the infection noted. While the mesenteric glands were swollen they did not present the appearances of primary buboes.

Wilm[1] examined a large number of pest cadavers in Hong Kong. Especial attention is drawn to the involvement of the gastro-intestinal tract. The solitary and agminated intestinal lymphoid nodules were generally swollen and hemorrhagic, and the mesenteric glands were found swollen, softened, and mottled with hemorrhages. Wilm claims to have found in 20 per cent. of the cases without external buboes that the stomach and intestines were predominatingly affected. This observation thus far stands alone and in opposition to the experiences of other writers.

The two main types of the plague—the bubonic and pneumonic—may be considered as established by the observations made during the present epidemic. Additional confirmation of the studies in China and Hong Kong has recently come from Japan[2] and Sydney, N. S. W.[3] Viewed by the light of the experiences in other places where the plague has gained even a temporary foothold, the absence of the pneumonic disease from San Francisco is the more remarkable. In all places where plague has secured a start evidences of rat infection and probable rat dissemination have been brought forward. It is, therefore, the more strange that in San Francisco, even after a year's prevalence among the Chinese, no evidence of a similar infection of vermin has been obtained. An attempt was made by the National Commission to determine whether the rats in Chinatown harbored the plague. Only one dead rat was obtained for examination, and it proved negative. This animal showed signs of traumatism about the

[1] Ueber die Pest-epidemic in Hong Kong in Jahre 1896, Hygienische Rundschau. 1897, Bd. vii., Nos. 5 and 6.

[2] Kitasato. Bericht über die Pest-epidemic in Kobe und Osaka, Tokio, 1900.

[3] Report of the Outbreak of Plague at Sydney, 1900.

body, and may have been killed by a dog or by other violence. About one dozen rats were caught in traps in the sewers in the Chinese quarters. They were fed and kept under observation for about two weeks, during which time only one died. Upon examination this animal gave a negative anatomic and bacteriologic result. The others were killed, but not examined.

It is, therefore, safe to assume that no considerable if any spread of the plague due to the rats in Chinatown has taken place. And it seems not unjustifiable, judging from the experiences of other infected places, to ascribe the limited and localized character of the San Francisco outbreak to the present immunity of the rat population.

A comparison of the natural disease in man and the experimental disease in guinea-pigs, as they appeared in San Francisco, with the descriptions of the natural and experimental disease as observed in other places, will supply immediate conviction of the identity of the pathologic processes. The gross lesions are characteristic and unmistakable. Moreover, the main features of the natural disease in man and the rat are easily and constantly reproducible by experimental inoculation. The histology of the lesions in man and animals is also in considerable accord. The primary buboes are practically identical; the necroses in the liver and spleen are easily comparable, and while, however, the proliferative nodules in the spleen, liver, and lungs in guinea-pigs may not have an exact counterpart in man, perhaps closer study of the pyemic (metastatic) lesions in man may show that beside necrosis and suppuration, considerable cellular proliferation has taken place. The minute changes in parenchymatous, proliferative, and emigrative cells—degenerations, necroses, etc.—are indistinguishable in man and animals.

When, therefore, the pathologic anatomy, bacteriology, and the results of experimental inoculations are carefully considered, it is not easy to see by what means a part of the medical profession of San Francisco was and continues to be misled as to the nature of the epidemic disease prevailing in the Chinese quarter of that city. It is, however, due to the profession of San Francisco to state that this small number was far outweighed by those physicians who were convinced that the pest existed, and expressed themselves accordingly. Among these were the bacteriologists and pathologists of the city almost without exception.

In conclusion, it is a pleasure to acknowledge the many favors conferred upon the National Commission by the local medical profession of San Francisco, and the great assistance in the scientific pursuit of the work rendered by Drs. Williamson, O'Brien, and Kellogg, of the City Board of Health, and Dr. Wilson, district physician.

THE BACTERIOLOGY OF BUBONIC PLAGUE.

By FREDERICK G. NOVY, Sc.D., M.D.,
OF ANN ARBOR, MICH.

SINCE the studies of Yersin upon plague, in 1894, the bacteriology of this disease has been the subject of numerous exhaustive investigations, not only by independent workers but also by special Commissions which European governments, namely, Austria, Germany and Russia, have sent to India. As a result the biologic properties of the bacillus pestis and its effects upon experimental animals are well known.

In a remarkably short time the chief etiologic factors in bubonic plague have been revealed and effective means have been provided in Haffkine's vaccine and Roux-Yersin's serum which, together with careful isolation and thorough disinfection, have rendered it possible to check the spread and even to cure this disease. There are, however, many questions in the epidemiology of plague which still await a satisfactory explanation. It is not the purpose of this paper to enter into the consideration of such questions, but rather to present the bacteriologic studies made by the United States Commission in San Francisco together with subsequent experiences with the plague bacillus at Ann Arbor.

Owing to the manifold clinical features presented by plague it will be readily seen that the greatest importance attaches to the demonstration of the presence of the pest bacillus. As is well known, the most common type of the disease is that in which there are more or less marked enlargements of the lymphatic glands. Such buboes are usually met with in the femoral or inguinal regions, less frequently in the axillæ or in the neck. A well-marked bubonic case of plague offers no difficulty in the way of diagnosis. But on the other hand it must be remembered that there are cases of plague, septicemic in

character, where little or no glandular enlargement can be detected. An instance of this kind was met with by the Commission where, although the patient (Case VI.) was seen during life, it was only after the bacteriologic examination of the spleen, and more particularly the positive animal experiment, that it was shown to be a case of plague. The pneumonic type of the disease was not met with by the Commission.

The detection of the plague bacillus during life is possible, but at times rather difficult. In the case of a well-defined bubo it is feasible to introduce a hypodermic needle, and in this way remove a few drops of the fluid from which cover-glass preparations and cultures may be made, and in the experience of the German Plague Commission such procedure frequently revealed the presence of large numbers of plague bacilli. At San Francisco in one living case the attempt was made to detect the plague bacillus in this way. The result in that case was negative both culturally and microscopically. The failure was undoubtedly due to the fact that the needle did not actually pierce the small gland. In suppurating, discharging buboes it frequently happens that either the pus will be perfectly sterile or it will contain only streptococci and other pyogenic organisms.

In very severe forms of plague, and of course in the septicemic type, plague bacilli are present in the blood. A few drops of blood taken from the finger or from the ear lobe can be used for an examination. The number of bacilli in the blood during life is necessarily small, and for that reason their detection by direct microscopic examination is very difficult. In the experience of the German Commission frequently where the cover-glass preparations gave negative results the cultural methods were successful. Of 124 cases thus examined 81 gave negative results. It is evident, therefore, that a mere examination of the blood cannot be relied upon as a means of diagnosis. The case already mentioned, where an attempt was made to discover the plague bacilli in an enlarged gland two days before death, was also used for a blood examination, but with equally negative results. Only a drop of blood was used in this trial, and it is quite probable that if one or two cubic centimeters of blood had been drawn from a vein by the aid of a syringe, and the amount spread over a series of agar tubes or over agar plates, the result might have been otherwise.

While there is more or less uncertainty in the detection of pest bacilli *intra vitam* in the enlarged glands and in the blood of plague patients, no such difficulty is experienced in the pneumonic form of the disease. The blood-streaked sputum in such cases is, according to the experience of numerous observers, invariably rich in bacilli. A case of primary pneumonic plague which resulted from accidental laboratory infection was recently under my observation, and in this instance a microscopic examination gave an early and definite diagnosis.

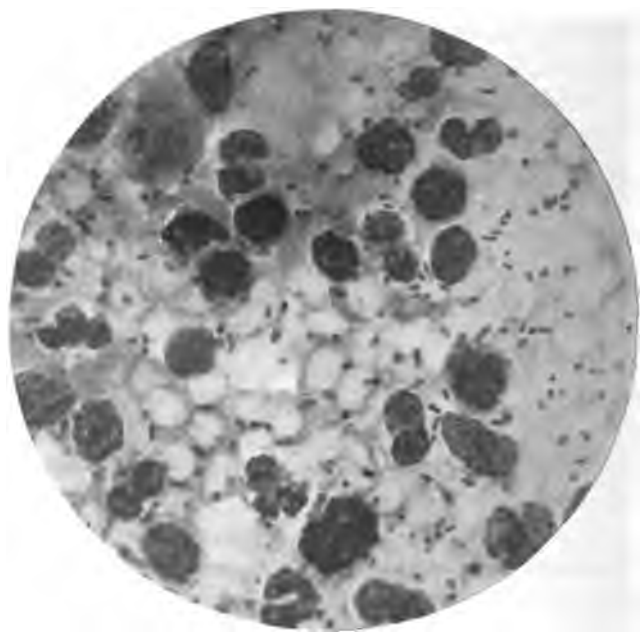
In the investigation at San Francisco the Commission was fortunate enough to meet with six cases of plague. Three of these were seen during life, and the other three were not seen until after death. In not one of these cases did the attending physician, whether Chinese or white, call the attention of the city Board of Health to the possibility of plague being present. Indeed, this has been the history of nearly all the known plague cases in San Francisco. It was in view of the difficulty of obtaining reliable reports from the Chinese as to their sick, as well as the difficulty of making satisfactory diagnoses of plague during life or even postmortem, that led the Commission to formulate a recommendation which seemed to them of the very greatest importance. It was recommended that every Asiatic who had fever should be suspected as a case of infection with plague until the disease was proved to be other than plague, and every dead body should be treated as a plague cadaver until a bacteriologic examination had proved the absence from the body of the bacillus pestis.

A bacteriologic examination of the enlarged glands, if there are such, should be made. In several of the bodies examined at San Francisco the glands contained enormous numbers of pest bacilli, whereas in others they were less abundant. On the other hand, the spleen in five out of six cases was exceedingly rich in plague bacilli, and in only one case (Case VI.) were these present in such small numbers as to be easily overlooked in a cursory examination. Nevertheless, a guinea-pig inoculated with this spleen died in the usual time.

This experience indicates the necessity of recourse to animal inoculation whenever the microscopic examination fails to give a direct and unequivocal answer. In this connection I may cite the expe-

rience of the German Commission, which by means of the animal experiment repeatedly demonstrated the presence of plague bacilli, although microscopically and culturally they could not be detected.

Streak preparations from the spleen or glands were usually stained with Loeffler's methylene blue or with carbolic thionin. Where care is taken to avoid overheating the specimen while fixing little difficulty is experienced in obtaining the characteristic bipolar stain. Inasmuch as methylene blue is likely to overstain, it should not be allowed to act for more than a few seconds. A typical preparation from a plague



case will show enormous numbers of pest bacilli which are invariably single. (See Figure.) These should be examined under as high a power as possible. A 1/12 oil-immersion objective and No. 4 eyepiece will show clearly the rounded ends of the short, thick bacillus, and in addition will bring out definitely the bipolar character. As is well known the plague bacillus is not stained by Gram's method.

The typical short, thick bacillus is the only form met with when perfectly fresh organs of man or of animals are examined. When, however, the autopsy was delayed for some hours after death, as was

not infrequently the case, a peculiar modification was to be seen. A preparation made from such material would show beside the usual bacilli large, oval, or roundish bodies, which may be considered as involution forms. These peculiar modifications, as a rule, do not stain evenly, but instead show a light center surrounded more or less completely by a deeply stained ring or border. Because of this peculiarity they have been spoken of not inaptly as "dough-nuts." These degenerative forms were met with in considerable number in several of the cases studied by the Commission, and were absent in but one instance (Case VI.). It may be stated incidentally that the German Commission met with these same degenerations in Bombay. As already indicated the "dough-nut" form can be produced in animals, provided these be kept for twelve to twenty-four hours in a warm place. As is well known the plague bacilli are remarkably prone to develop roundish, pear-shaped, or yeast-like involution forms on dry and especially on salt agar.

The isolation of the plague bacillus from the fresh cadaver offers, as a rule, no special difficulty. It is very important to have a slightly alkaline medium, inasmuch as even a faint acidity exerts a marked inhibitory effect. This fact is often demonstrated in the laboratory in a most unwelcome way, when such media after profuse inoculation with unquestionably viable cultures show no sign of growth. Agar plates or tubes streaked with fresh tissue invariably yield good growths, provided that the number of pest bacilli in such tissue is not too small. When only a few organisms appear to be present it is advisable to use a larger amount of material for inoculation. As a matter of fact, even when the tissues are extremely rich in pest bacilli, the number of colonies which develop on agar is often considerably smaller than might be expected, showing that many of the organisms are considerably enfeebled. This condition is especially met with when tissues are derived from animals which have been dead for many hours. The involution forms which are present in such cases are apparently incapable of development on artificial media.

The inoculation of such material, however, into a susceptible animal will cause death, and from the fresh organs thus obtained cultures can be readily secured. As will be indicated presently the guinea-pig can hardly be considered as among the most susceptible animals.

The cultural characteristics are well known and need not be elaborated upon in this connection. They are, moreover, described, though briefly, in the appendix.

For the purpose of diagnosis the direct microscopic examination is, as a rule, sufficient. When, however, the pest bacilli are very few, or when other organisms are present which tend to mislead in the identification, it is then necessary to resort to animal inoculation in order to arrive at a satisfactory conclusion. A portion of the gland or spleen should then be introduced under the skin of an animal. The common rat, in the experience of others, is by far the most susceptible animal, and should be used whenever possible. Inasmuch as rats were difficult to obtain at San Francisco, the experimental inoculations were confined to guinea-pigs, which usually died in from three to five days after such inoculation. Exceptionally, a guinea-pig may die in thirty-six hours or even less, and I have repeatedly observed death to be delayed for ten or twelve days. This is especially true when pure cultures, rather than bits of tissue, are introduced into the animal. It may indeed happen that pure cultures, recently isolated from man or animals will fail to kill guinea-pigs.

The failure, at times, of pure cultures of pest bacilli to kill guinea-pigs indicates in the first place the labile character of the virulence of these organisms when grown on media which have an even slightly unfavorable composition or reaction. Moreover, it shows that the guinea-pig offers considerable resistance to infection and that the survival of such an experimental animal does not positively exclude the presence of plague bacilli. The virulence of these organisms can often be restored by frequent transplantation to fresh, distinctly alkaline media, and especially by the use of the collodium sac method.

The effects observed in guinea-pigs varied somewhat with the duration of the disease. Where death occurred in less than two days little or no structural change was observable. Usually, as a result of subcutaneous infection, the inguinal or axillary glands were considerably enlarged. Inasmuch as the changes which take place in the glands, spleen, and other organs will be treated by Dr. Flexner it will be unnecessary to describe these in this connection. I may add, however, that exceptionally well-marked pneumonia occasionally, though rarely, may be observed in guinea-pigs following subcutaneous injection. In one instance recently observed, the pneumonic process

was associated with pericarditis the pus of which yielded a pure culture of plague bacilli.

The direct detection of the plague bacilli in the tissues of the six cases studied in San Francisco, the cultural properties of the organisms isolated from these cases, and the successful animal inoculations demonstrated the existence of the plague in that city. If any additional proof as to the nature of these organisms and of the disease existing there was necessary, it has been recently furnished by the accidental development of a case of acute pneumonic plague in one of the workers in the hygienic laboratory of the University of Michigan. The young man referred to had been engaged for some months in the preparation of Haffkine's vaccine and Lustig's serum for Parke, Davis & Co., of Detroit. A highly virulent California culture was employed in this work. In some unknown way, possibly through the use of a pipette or soiled finger, the organism was introduced into the mouth, and a very acute infection followed. The young man was taken sick Wednesday evening, April 4th, and complained of intense backache. The temperature rose in a few hours to 102° and more. Toward morning he vomited twice a greenish, bile-stained fluid. At noon that day I learned for the first time of his illness, and, with Dr. Vaughan, visited him in the afternoon. When seen his temperature was 102.8°; his eyes were bloodshot and he complained of severe headache, the pulse was rapid and the pulmonary distress was marked. It was clearly a very severe acute infection, and, knowing the kind of work he was engaged in, it was decided to give him at once an injection of Yersin's anti-pest serum. Twenty c.c. of this serum was given at four o'clock that afternoon. At the same time the tonsils and the inside of his mouth were rubbed with swabs, and the material thus obtained was planted on agar and cover-glass preparations were also made. These showed a large number of ordinary mouth germs, but nothing that could be identified as plague bacilli. The cultures, it may be added, when developed were likewise negative, and when injected into a guinea-pig had no effect. At eight o'clock in the evening the patient coughed up for the first time a small bit of blood-stained sputum. This was examined at once and on staining showed plague bacilli. Accordingly the patient was removed immediately to the isolation hospital and his room was locked up and thoroughly disinfected with formaldehyde.

After arrival at the isolation hospital, with the knowledge that we had to deal with a case of acute primary pneumonic plague known to be almost invariably fatal, intravenous injections were decided upon as offering the only possible chance for recovery. Accordingly twenty c.c. were injected intravenously at about eleven o'clock that night. The next morning, the temperature still persisting at about 104°, a second intravenous injection of like amount was given. Even this showed no marked effect, and as the temperature reached 105.3° at one time and the patient was becoming markedly apathetic a third injection was made. This time 20 c.c. were injected intravenously and 40 c.c. subcutaneously. All told he received within twenty-four hours after he was seen by us 120 c.c. of serum, one half of which was injected intravenously. Within a few hours after the last injection the temperature dropped to 100°, and before the end of the third day of his illness it reached the normal. With the exception of an attack of heart failure caused by his attempt to sit up on the fourth day and the serum effects, such as swollen joints and hives which developed a week later, the patient made a complete recovery. Extreme cardiac weakness was a noticeable symptom which persisted for more than two months after the onset of the disease.

It should be added that the animal experiment eventually confirmed the original microscopic diagnosis. A guinea-pig inoculated with the sputum raised at the end of the first day (Thursday evening) died in four days of typical plague. It is further noteworthy that a second guinea-pig inoculated with sputum rich in plague bacilli which was raised Saturday morning after the temperature had fallen remained alive.

Appendix.

Under this head I have placed the description of the bacteriologic work done on the six cases of plague which were studied by the Commission. It should be stated that this matter forms part of the report of the Commission as published in the "Public Health Reports" of the United States Marine Hospital Service.

Case I.—Chun Ah Chou, 814 Washington Street; necropsy February 5th. The spleen and left femoral glands were examined. These organs were found to contain enormous bodies of bacilli having the morphologic and tinctorial properties of bacillus pestis; thus, the short, thick, oval rods gave a bipolar

stain with Loeffler's methylene blue or with carbolic thionin and were decolorized by Gram's method. Their pathogenicity was determined by inoculation of portions of the spleen and of a pure culture subcutaneously into guinea-pigs.

Agar streaks made from the perfectly fresh organs showed many small, white, moist, isolated colonies, having all the appearance of those of bacillus pestis. This was further confirmed by microscopic examination of living and stained preparations of such cultures. A few rapid-growing colonies due to other forms of bacteria were present. Subcultures were made in glucose, gelatin, bouillon, agar, salt agar, agar and milk. On agar in Petri dishes in twenty-four to forty-eight hours in the incubator, small, white, or grayish, moist colonies developed. These had finely granular centers, with a smooth, sharply-defined border.

The stab culture in glucose gelatin developed a slight growth along the line of inoculation. On the surface the growth spread slightly, was grayish, moist in appearance, and had a slightly wavy, raised border. No gas was formed.

In bouillon, in twenty-four hours, a diffuse cloudiness was produced. The sediment was very slight, scarcely appreciable. Subsequently a faint stringy deposit formed. The surface remained perfectly clear, with a trace of a ring or collarette.

The streak cultures on nutrient agar presented a moderate grayish-white, moist growth which, when touched with a platinum wire, could be drawn out into strings.

On 5 per cent. salt agar the growth is very slight, scarcely visible, and shows the peculiar roundish or pyriform involution forms of the pest bacillus.

In milk the organism grows without producing any visible change in the medium.

The absence of gas production and of coagulation of milk, together with the macroscopic and microscopic characteristics, agreed fully with the properties of bacillus pestis.

Guinea-pig No. 1. Was inoculated under the skin with a portion of the spleen from the above case. It died in thirty-six to forty hours. Cultures on agar made from the spleen and heart's blood gave almost pure growths of the pest bacillus. Direct examination of the organs showed enormous numbers of typical plague bacilli.

Guinea-pig No. 2. Was inoculated subcutaneously with a pure culture obtained from the gland of the above case. The animal died in three days. Plague bacilli were very numerous in the spleen and inguinal glands, and were also present in the heart's blood.

CASE II.—Lum Hong Yuen, 28 Ross Alley; necropsy February 6th. Smear preparations from the spleen showed large numbers of short, thick rods, chiefly single; some oval or roundish forms were also present. The organisms stained readily with Loeffler's methylene blue or with carbolic thionin. In the latter case the bipolar staining was excellent. The organisms were

completely decolorized by Gram. Cover-glass preparations from the gland likewise showed very numerous bacilli, occurring singly, taking the bipolar stain, but not that of Gram. Agar cultures were made at the time of the necropsy in the undertaker's shop of Main Fook. The cultural and morphologic characteristics were the same as those observed in Case I.

Guinea-pig No. 3. Received subcutaneously a portion of the spleen from the above case; died in five and one-half days. On autopsy the spleen was found markedly enlarged, full of white nodules, which were also present in the liver and in the lungs. Cover-glass preparations from the spleen showed enormous numbers of bacilli, having all the characteristics of bacillus pestis. Agar slants were inoculated with the heart's blood and spleen of this animal. The former yielded a slightly contaminated growth, but the culture from the latter was pure.

CASE III.—Wong Chi Lui, 21½ Waverly Place; autopsy February 7th. Streak preparations from the spleen showed very numerous pest bacilli apparently in pure culture; the predominating form was the short, thick rod, although some oval or roundish forms were present. Loeffler's methylene blue and carbolic thionin stained the bacilli readily, demonstrating the characteristic bipolar form. The organisms were completely decolorized by Gram. Similar preparations made from one of the left femoral glands show fewer organisms; but these in form, size, and staining reactions are identical with those found in the spleen. Cultures made on agar developed very slowly; on subsequent transplantation, however, the growth was more rapid, more abundant, and typical of that of bacillus pestis.

Guinea-pig No. 4. Was inoculated subcutaneously with a portion of the gland from the above case. Death resulted in three and one-half days. Bacilli were numerous in the spleen and corresponded in characteristics to those of the plague bacilli.

Guinea-pig No. 5. Was inoculated subcutaneously with a portion of the spleen. It was found dead three and one-half days later. Numerous plague bacilli were found in the spleen, heart's blood, and glands. Agar streaks from the heart's blood gave numerous small colonies of pest bacilli with a few larger colonies due to foreign organisms. The spleen gave numerous isolated small moist colonies, apparently a perfectly pure culture of the plague bacillus. Agar-streak plates were made at the same time, and gave in twenty-four hours numerous minute colonies.

Guinea-pig No. 6. A portion of the spleen from this case was introduced into the peritoneal cavity. Death resulted in four and one-half days. Pest bacilli were abundant in the internal organs and in the glands. Agar streaks from the heart's blood gave a very limited growth, while that from the spleen was scarcely visible. In this and several other instances difficulty was experienced in starting the growth of the organism directly from the tissues. Once started, however, with subsequent transplantations better results were obtained.

Guinea-pig No. 7. Was inoculated subcutaneously with a loopful of a pure culture obtained from guinea-pig No. 5. It died in two and one-half days. Necropsy revealed a hemorrhagic edema, and cover-glass preparations of this showed pest bacilli mixed with numerous minute diplococci and streptococci. The spleen was large and soft, contained nodules, and, on staining cover-slips therefrom, enormous numbers of typical plague bacilli, apparently perfectly pure, were found. No diplococci were present.

CASE IV.—Tom Shom, 814 Washington Street; necropsy February 11th. During life some fluid was aspirated by means of a sterile syringe from the swelling in the right femoral region and transferred to nutrient agar. Blood was also drawn from the lobe of the ear and planted on agar. Stained preparations made from these specimens failed to demonstrate the presence of any organism. Cultures developed pyogenic cocci, but failed to give any indication of pest bacilli. On necropsy the femoral glands, though characteristic of plague, were found not markedly enlarged. It was evident that the aspirating needle, when introduced, had missed the gland proper, and the failure to isolate the pest bacillus during life in this can thus be explained. It should be noted that the periglandular tissue was but very slightly involved. Streak preparations made from the hemorrhagic gland showed relatively few typical plague bacilli. A long, thick bacillus was present in small numbers. Gram's stain was negative. Streak preparations from the spleen showed the pest bacillus to be present in large numbers and apparently pure. The organisms occurred singly, gave the bipolar stain, and were decolorized by Gram.

Guinea-pig No. 8. Was inoculated subcutaneously with a portion of the spleen from this case. Six and a half days later, though healthy in appearance, it was killed. A circumscribed caseous local lesion was found. There was a slight glandular enlargement on the same side. The spleen was slightly enlarged and showed white nodules. Pest bacilli having the short rod and oval form were present in small numbers.

CASE V.—Ung Ah Buck, St. Louis Alley; necropsy February 12th. Cover-slip preparations from the cervical lymph glands showed the presence of several distinct organisms. The short, thick, oval forms of the pest bacillus were present in small numbers. With them was associated a large, thick bacillus; there were also bacilli present resembling the bacillus diphtheriæ and a diplococcus closely resembling that of Fraenkel. The pest bacilli gave the usual bipolar stain with methylene blue and with carbolic thionin. Specimens stained by Gram's method showed deeply stained diplococci, the other forms being decolorized. Smear preparations from the spleen showed many organisms resembling the bacillus pestis morphologically.

Agar streaks from the fresh spleen gave a number of discrete moist colonies, which consisted of large, oval, non-motile bacilli, occurring singly and only occasionally in pairs; the streak cultures from the cervical gland also

gave numerous isolated colonies. In both cases the cultures obtained were apparently perfectly pure and agreed in every respect with the plague bacilli. The other bacteria seen in cover-slips did not grow. Agar plates yielded the same results.

Guinea-pig No. 11. Was inoculated subcutaneously with a small portion of the spleen from the above case. In about three days the animal was very sick, and was finally killed five and one-half days after inoculation. Bacillus pestis was found in the spleen and to a less extent in the blood.

CASE VI.—Foong Ah Fong, 747 Sacramento Street; necropsy February 12th. Streak preparations from the spleen revealed the presence of pest bacilli, although these were not very abundant; indeed, they were difficult to find in cover-slips. Typical bipolar staining rods and oval, roundish forms were, however, found. Gram's stain was negative.

Streak cultures were made with the fresh spleen on agar slants, and at the same time agar plates were made. The agar streaks failed to give an appreciable growth, but on the plate a colony was found which corresponded to that of the plague bacillus. On microscopic examination it was observed to consist of small, short, oval, non-motile rods, which decolorized by Gram. The colony transplanted to agar gave a typical growth of pest bacilli, and this culture was used to inoculate guinea-pig No. 10.

Guinea-pig No. 9. Received a portion of the spleen of Foong Ah Fong subcutaneously. It died in four and one-half days. The spleen contained enormous numbers of pest bacilli, which stained in the usual bipolar manner and were decolorized by Gram. The heart's blood likewise contained the organism. Cultures were made on agar from the spleen and heart's blood of this animal; both gave numerous small, moist colonies of bacillus pestis.

Guinea-pig No. 10. Was inoculated subcutaneously with the agar culture mentioned above. It was killed two and one-half days later. The spleen showed only a few but characteristic pest bacilli. Under the skin there was but slight local change, and a few typical bacilli were found.

The bacteriologic examination of the foregoing six cases has, therefore, demonstrated the presence of the bacillus pestis in each.

DISCUSSION.

DR. STERNBERG: I only want to say a word that occurs to me at this moment, and that is that if this thing had occurred thirty years ago we would probably be reading in the morning papers of 500 deaths a day in San Francisco and of the spread of the disease to other parts of the country. If we had had to depend upon the local physicians, and especially those of thirty years ago, there is no reason to believe that the experiences of the past century would not have been repeated in this. The prompt suppression of the epidemic is due to the fact that we have well-equipped pathologic laboratories in various parts of the country and trained bacteriologists who were available to determine the nature of the prevailing disease and to give advice as to the best method of restricting its progress.

DR. PARK: A very brief report of two cases of plague may be of some interest. You will probably remember that a coffee ship recently entering port at New York was reported to have plague aboard. When I visited the ship and asked for the sick persons the captain and cook walked into the cabin. Both had buboes in the groin—one with distinct abscess, the other simply enlarged glands. The needle brought pus from one and bloody fluid from the other, and both contained very few bacilli. Both cases got perfectly well, and it was interesting to note the remarkably light form of the disease, similar to that referred to by Dr. Barker.

I would like to ask if the serum is of value in the late cases?

DR. SHATTUCK: I would like to ask how soon the bacilli appear in the urine, because we know that in typhoid fever their appearance is a late manifestation?

DR. VAUGHAN: I desire to compliment the readers of the papers for the most excellent *résumé* of the subject they have given us. It may not be out of place at this time to say a few words about the initial symptoms of the case we recently had at Ann Arbor, and of the care taken to prevent the spread of the disease. The young man who became inoculated with the plague bacillus is the only student whom we have ever allowed to work with this germ. In July, 1900, he made a request that he be allowed to do some work with the plague bacillus. He was given a culture which Dr. Novy had brought from the Pasteur Institute some years ago, and which had largely lost its virulence. On Dr. Novy's return from California this young man began work with one of the cultures which Dr. Novy brought with him, and soon succeeded in infecting himself. About nine o'clock on the evening of

a certain day a fellow-student telephoned me that Mr. Hare (the name of the young man who became infected) was passing a renal calculus. I asked how he knew the diagnosis was correct, and he replied that Hare had once before passed a calculus and recognized the character of the pain. On further inquiry I learned that Hare had at that time a temperature of about 102°. About two o'clock the next morning Hare's chum telephoned me that Hare's temperature had risen to 103°. I still did not suspect infection with the plague bacillus, and asked that Dr. Spitzley be requested to see him. Dr. Spitzley went to see the young man and made a provisional diagnosis of pleurisy. The next day I suggested to Dr. Novy that we should go to see Hare. We found him with a temperature of 104° and coughing up mucus. Dr. Novy took some of the expectoration to the laboratory and detected in it plague bacillus. I immediately had the isolation ward near the hospital buildings lighted and heated, and that night we took Mr. Hare and the two young men who had been with him to the hospital. We locked his room and took the key with us. Later the room was several times thoroughly disinfected with formaldehyde gas. We cautioned the young men who remained with him concerning the disinfection of his sputum, which was always received in a solution of mercuric bichlorid. With due care I do not believe there is much danger in acquiring the disease while attending a patient suffering with this form of bubonic plague.

Dr. Dock: It may be of interest to pass around the temperature-chart of this case and to add a few words about the clinical signs. When first examined the night after he was taken sick the patient had a slight friction sound on the right side, but the next day there were no physical signs on that side. There was a marked dulness on the left side, with a few friction sounds, diminished respiratory murmur, and a few piping râles. The physical signs reminded one rather of a case of latent pneumonia with more or less dulness, but without marked auscultation signs. Later on the friction sounds reappeared at intervals for a week over various portions of the left pleura. The aspect of the patient was highly characteristic—notwithstanding the slight physical signs he presented the appearance of severe illness, with a combination of apathy and restlessness and frequent changes of position. The pulse was dicrotic, but it was not very marked, probably because when I first saw him he had already taken two doses of serum. The spleen was not enlarged until the third day, reaching two inches below the ribs, hard and thick, and gave a great deal of pain. The sputum was characterized by being less sticky and more bloody than that of pneumonia, and with enormous numbers of germs. The heart weakness was quite characteristic of plague. The patient felt perfectly well on the sixth day, but I was suddenly called later to see him because of difficult breathing, with pain, such as he had just before the spleen complication came on. I found that he had gotten out of bed, was sitting in a chair, reading, was still delirious, his pulse hardly perceptible, the

heart beating feebly, about 50 per minute, and it looked as if he would die of heart failure. He got over it, and steadily improved, but his heart was weak for some days. On the tenth day he had hives, with pain in the joints and some rise of temperature; other than that he presented no evidences arising from the serum.[1]

DR. WELCH: Were any prophylactic injections made on other persons?

DR. DOCK: Yes, sir.

DR. WELCH: Were there any bad symptoms:

DR. DOCK: Yes, in two of eight cases; but the injecting fluid used in those two cases came from two bottles, the other halves of which caused no discomfort to the persons who took them. The two persons had urticaria, with pain about the joints, but no swelling. The pain was severe, but there was nothing alarming about the condition. In the first case the trouble was supposed to have arisen from food intoxication, but when the symptoms appeared in the second case we recognized its cause. The symptoms, of course, did not depend on the antitoxin, but were like those occasionally caused by horse-serum of various kinds.

DR. BARKER: In reply to Dr. Park's question, I may say that I have had no personal experience with the serum, and my statement was based upon the report of the Russian Commission. The same may be said in reply to Dr. Shattuck. I do not know how early the bacilli appeared in the serum.

DR. FLEXNER: I may answer that question with some indirect evidence. They have been found in the urine of patients who died on the third or fourth day of the disease, and it seems probable from this that they appear early in the disease.

DR. BARKER: I want to add that probably all cases of bubonic plague are contagious, some directly, some indirectly. The most contagious form, of course, is the pneumonic, and such patients should have their mouths covered by a fine veil, and anyone going near them should keep his mouth and nose covered with a fine sponge. The making of an autopsy is by no means a safe procedure, and there is danger in attending plague cases. This is proved by the number of physicians and investigators who have become infected.

In regard to the San Francisco situation, I would like to emphasize the importance of the work done by Drs. Kellogg and Kinyoun. The whole

[1] Note on revising proof, May 18, 1901: "The patient still has marked heart weakness, becoming dyspneic, with pain in the heart region on slight exertion."

country owes a deep debt of gratitude to those pathologists, and I may say, in addition, that every pathologist in San Francisco, except possibly one, agreed that this disease was plague, while those who opposed that view were men without sufficient training to recognize it.

We ought to congratulate Ann Arbor on the prompt work that saved the patient's life and prevented the spread of the disease. When we remember that the pneumonia cases have a mortality of about 100 per cent. we can appreciate the importance of their prompt and successful action.

SLOW PULSE, WITH SPECIAL REFERENCE TO STOKES-ADAMS DISEASE.

By ROBERT T. EDES, M.D.,
OF BOSTON.

SINCE our late associate, D. W. Prentiss, was so kind as to call my attention to his patient with an extremely slow pulse, whom he showed to this Society in 1889, and in whose case I had the opportunity to make a postmortem examination, I have added somewhat to my own experience, and have also looked over a not inconsiderable amount of literature which has accumulated upon the subject since that time.

CASE I.—Mrs. Rosetta M. P., aged fifty years; housewife; born in New Hampshire, of New England parentage. Her father died of pulmonary hemorrhage; her mother from a fall during pregnancy. She has been an invalid since the birth of a child twenty-five years ago. She has had one miscarriage and frequent headaches; one year ago these were intense. In the Worcester City Hospital a short time last year; was short of breath, emotional, and fainted several times. In January she fell on the street. Two years ago she had sciatica. She was lately treated by Dr. Samuel Breck for uterine trouble. Fainted one day while at work, and has fallen in the house several times since then.

Entered the Boston City Hospital June 3, 1897. While in bed she has sinking spells; feels as if she were falling. Appetite fair; bowels constipated; temperature 101°; pulse 56; respiration 20. Patient said that her nervous condition was due largely to shock and grief at the death of her daughter's child of scarlet fever. She was pale, anemic, and nervous, the pupils equal, reacting to light and accommodation. The tongue moist, with a white coat. The pulse regular, 40, of poor strength and volume. The heart's area not enlarged, action irregular, sounds very weak. At times, between pulsations, are heard sometimes one, sometimes two or three slight sounds, as of incomplete beats. Pulse synchronous with heart. At times a soft systolic murmur replacing the first sounds at the apex, slight roughening of the first sound at the aortic area. Lungs and abdomen negative; knee-jerks normal; no ankle clonus hyperesthesia of the extremities.

June 4th. Felt faint during the afternoon, dull and heavy headache; pain about the heart and throbbing of the head. Several slight sinking spells

during the early part of the night. About 1 A.M. she screamed and apparently lost consciousness. The night nurse could not feel her pulse. House officer called and gave her subcutaneous injections of ether; patient aroused, confused, but recognized the house officer. Pulse very weak and slow. Quiet the rest of the night. Next day she felt weak and very dull. In regard to the attack of the night before, she said that she was not unconscious, but she felt powerless, and screamed because she felt herself sinking; felt as if oppressed by a great weight. Dark blurring of the eyes; was conscious of the night nurses, and heard them discuss as to whether she were dead. Recognized house officer when he came. On this day the pulse went down to 20.

11th. Patient says that she can feel the pulsations of her heart in her left hand and arm when grasping anything with this hand. Pulse and heart sounds synchronous, no evidence of organic disease. Patient feels very weak.

19th. Patient up, dressed, and out on the piazza. Pulse still weak and slower than the apex.

24th. Pulse ranged from 35 to 48. Has had a slight chill; attack of vertigo every few days. Pulse at such times scarcely perceptible; does not lose consciousness when in these attacks. Never any convulsions.

29th. Had four spells yesterday; she was given brandy and nitroglycerin; attacks of semi-consciousness preceded by headache, blurring of vision, feeling as if sinking down into a hole; she is somewhat paler than usual at such times, and her eyes are closed. After the attack she feels weak; head aches badly and she is much exhausted; pupils dilated and pulse slow (18 to 20), but improves with stimulation. She has her clothes on daily and spends an hour on the piazza. The attacks generally come on in the afternoon. Premonitory symptoms warn her to go to bed.

July 11th. Head heavy. Tenderness in the left side of the head.

13th. Condition much improved; pulse still slow. Discharged relieved. Diagnosis: hysteria, myocarditis.

The chart kept during this time gives the temperature on the day of entrance as 101° and for three days after as normal. After this it was not taken. The pulse after two observations at 20 rose somewhat, and ranged from about 25 to 48, being for a considerable part of the time between 35 and 45. The respirations were from 20 to 25.

Boston City Hospital, June 22, 1897. Urine: 500 c.c.; acid, 1012; urea, 1.39 per cent.; indoxyl normal; albumin slight possible trace; sugar, 0.

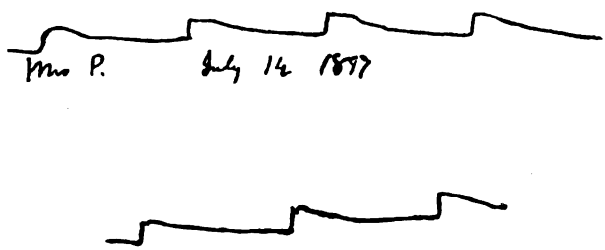
Sediment. Occasional abnormal blood globule; squamous epithelium; occasional small hyaline and finely granular cast; few blood and fat globules; few renal cells. J. B. Ogden.

Admitted to the Adams Nervine Asylum on July 14th. Her application paper gave nothing additional except the statement of Dr. Breck; she had lately had a thorough pelvic examination under ether without anything definite being found.

Height, five feet four inches; weight, 146 pounds. Early history unimportant, except the headaches. About seven weeks ago the headaches were worse and she had pain in the left groin. Seven weeks ago she fell several

times during the day with short spells of unconsciousness; the next day twice. When she entered the Adams Nervine she had not lost much flesh; her manner was calm, but she was sleeping badly, usually from one to five or six hours, seldom the latter. Her dreams were not especially bad, and she had no morbid fears or hallucinations; her appetite was deficient and she was constipated. She was pale, with a somewhat puffy complexion. She was frequently having the sinking spells. There was no enlarged cardiac dulness. Sounds nearly normal, the first sound rather long, occasionally with something like reduplication or interruption, occasionally a very slight beat just after the second. Says she feels her heart beat in her head and limb. Counted the head-beats herself while I held the radial pulse, and they were synchronous. Her hand goes to sleep. When she has the sinking spells the whole arm is involved. There is a burning sensation over the heart, and there is dyspnea when she lies upon her left side. The sphygmographic tracings have a long, flat top and gradual decline without dicrotism.

TRACING 1.



She continued in about the same condition for several weeks, with the pulse very slow, much of the time being 25 or 26, and at the paroxysms becoming imperceptible. The blood was never counted, but color-index was not below that of the average female. There was no abnormality in the white corpuscles. The urine, when measured, was below the normal in quantity, contained no albumin and only the normal amount of indoxyl. The eye-grounds were normal. There is a beating in the back of the head nearly all the time. The feeling coming from the back to the top of the head coincides with the spells. When seen in or soon after the attacks her pulse would be imperceptible or very slow; she said that in some of them she became unconscious, but this apparently did not last long. There were sometimes several days when there would be none. Her sleep improved somewhat as regards the average number of hours per night. The record of medication consists chiefly in cardiac stimulants, with no hypnotics.

September 10*th*. Patient has had several slight spells of faintness, occurring during the daytime; has been in bed ever since her entrance, but has a bed-rest; wants to get up; has complained of rheumatic pains in the muscles of both legs; pulse ranged from 32 to 36.

18*th*. On the 11th and 12th there were attacks (patient said afterward that she was not conscious during these attacks), during which the pulse was

scarcely felt at the wrist; duration fifteen to thirty minutes. On the 16th, about 9 o'clock, she had a fainting spell, and aroused dazed and confused. Again, about 1 A.M., she called the nurse and said that she felt she was going to have another attack, and while the nurse was at the telephone the patient screamed loudly several times, awakening and frightening all the patients. The nurse found her with eyes staring, pupils dilated, tossing herself about the bed and tearing her hair. No dyspnea, face very pale. The nurse tried to keep her quiet by holding her, assisted by the night watchman, who had been attracted by her cries. Assistant was called, but found the patient quiet but in an apparent unconscious state. Ammonia to the nostrils and subcutaneous injections of ether were given. Pulse ranged from 16 to 18; could scarcely be counted on account of weakness. Later on the nurse applied a faradic battery; patient began to scream again and kept it up for some time. Quieted down, and brandy, two ounces, and hot water were taken by the mouth.

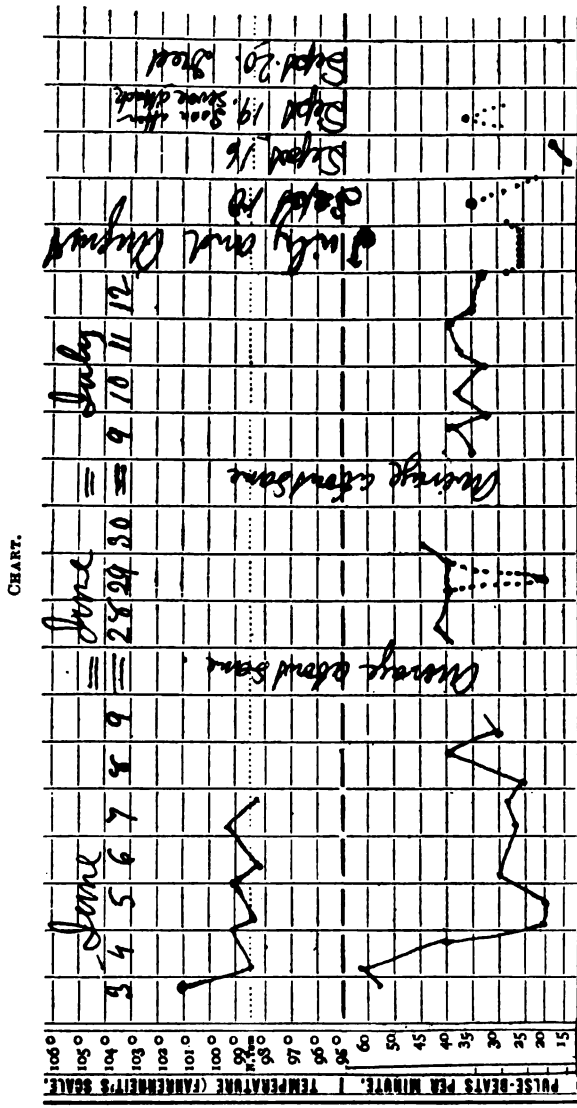
On the 17th the patient said that she felt she was dying the night before, and was unconscious of screaming. On this date she had several attacks during the day and night; all three attacks have been more severe than any before or since her entrance. Pulse at times is as low as 12 per minute. At other times during the attacks it could not be felt. This morning (18th) she seems better; has headache, and is very weak and exhausted; has not taken much nourishment.

19th. Attacks with difficult breathing (Cheyne-Stokes respiration), with extreme pallor and disappearing pulse, eyes staring, fixed apparently in unconsciousness; cold skin: no perspiration. This would be followed by a gradual return of pulse, at first a total suspension of respiration, a fairly rapid flushing of the face, return of respiration, some moaning, a moment or two of quiet, and soon a repetition to the cycle above described. These lasted for about fourteen and a half hours. Quieted down; color good; pulse 36; respiration regular and tranquil for about an hour and three-quarters. Two or three more attacks followed. Ether subcutaneously twice. Quieted down in about twenty minutes. Subcutaneous injections of brandy, ether, and strychnin were given in the above attacks, also hot brandy by the rectum. Milder attacks continued throughout the afternoon and evening. Between the attacks was languid, drowsy. Seen by Dr. Webber in consultation, who inclined to consider the trouble of nervous origin; a unique case; possibly absorption of the intestinal toxins. Advised general measures, cardiac stimulants, massage, and electricity.

20th. After the attacks of yesterday the patient's condition was considered dangerous, and family notified.

The assistant was called about 4 o'clock, being told the patient was dead; was informed on his arrival that the patient had been quiet and comfortable in the early evening. At about 8 o'clock a slight attack; others at 10 and 11 P.M., with intervals of short naps. At about 4 o'clock she aroused slightly, then suddenly stopped breathing; the pulse could not be felt. The patient was found reclining on the bed-rest, face pale, mottled areas like postmortem

appearance; no pulse felt; no heart sounds heard; extremities cold. Atropin subcutaneously among other stimulants. Pulse felt faintly; no other



From charts in Case I.

signs except a shallow respiration and an occasional soft sigh; after a while the sighs were only at intervals. Died at 6.15 A.M.

Autopsy by Dr. Councilman, September 20, 1897. Body well nourished; surface pale; subcutaneous fat abundant; slight edema of the posterior portion of both lungs; heart distended, especially the right side, with fluid blood; valves normal, save a slight thickening of the edge of the mitral valve; the myocardium normal; coronary arteries normal; the aorta smooth save for a few small plaques of atheroma in the beginning of the thoracic and above the bifurcation; both kidneys hyperemic; the capsule in places very slightly adherent; markings normal; the right kidney freely movable over an area of five inches; brain of normal size; convulsions well developed, rather pale, firm; arteries at the base of the brain were normal, as were all the cranial nerves.

Anatomic Diagnosis. Dilatation of the right side of the heart; old pleuritic adhesions; slight edema of the lung; chronic thickening of the mitral valve; very slight interstitial nephritis.

CASE II.—A man, aged eighty years, in fair general health, with a pulse said to have been usually about 68 or 70.

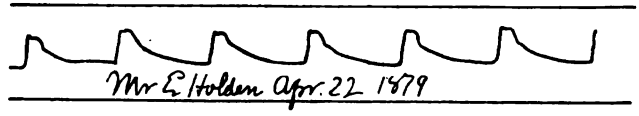
April, 1878. Had a slight bronchitis, with a pulse in the neighborhood of 33.

21*st*. Fell unconscious; vomited; pulse 26.

22*d*. Slighter attacks; vomited; there was no trace of paralysis; pulse 33, and most of the time from 32 to 36, and at times as high as 40; at times slight irregularity, with secondary beats.

23*d*. Severe attack.

TRACING 2.



24*th*. Another attack of unconsciousness; pulse 36. Cheyne-Stokes respiration, with complete pauses, during which there were some spasmodic movements. While the breathing was on the decline there were interpolated weak heart-beats, which disappeared during the period of apnea and increase. Apnea lasted about twenty seconds. There was a gradual improvement from this time. In June his pulse was 70, and on one occasion, after a little exertion, 80. In October of the same year his pulse was rather quick. About a year later he felt rather weak and the pulse was 36. In July he had another series of attacks, less severe than the first, with slow pulse and Cheyne-Stokes respiration. On one day it was noted that there were twenty-four large beats to the minute, each followed by a small one.

In November, 1880, he had a cold and cough, with breathing somewhat of the Cheyne-Stokes type, and a slow and very irregular pulse. An hour or two before he died the pulse was 44 and irregular.[1]

[1] Two sons of this patient died with interstitial nephritis. One of them had Cheyne-Stokes of the most typical form for several days before death. The wife of the other described to me,

In the sphygmograms, which in their general form were entirely of the usual character, there was occasionally to be found a very faint wave succeeding the main one.

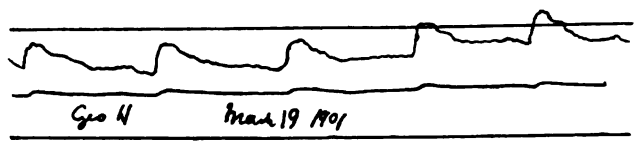
CASE III.—S. W., a Polish Jew, aged forty years, fainted at a meeting of some kind, and soon again. When he entered the Massachusetts General Hospital he had frequent fainting fits, with some convulsive movements. At the time my attention was kindly called to the case by Dr. J. J. Putnam he had had none for some time, and he was sitting up and about the ward. The pulse has been as low as 25, at first with intermediate slight beats. When I saw him the pulse was 38, strong, and there were no intermediate beats visible in the tracings, nor could I detect any by the ear. The interne of the service informed me that he had heard none recently.

CASE IV.—In September, 1899, I saw, with Dr. Edson, of Roxbury, a bank cashier, aged about sixty years. For years he had worked very hard, with very little vacation. Last winter he was restless and twitching, and he could not walk up hill as well as he used to. For years he had had occasional blind headaches. Last May he lost consciousness and fell. In July he had another severe attack, but after that none for a considerable time, until hot and tired in the cars. Since then several severe ones and a great many less so. In the severe ones he loses consciousness and twitches in face and legs. In the slighter ones there is no twitching, and no complete loss of consciousness. In the severe ones his color becomes white and then red, or red and then white, his wife stating the latter and others the former. During my visit he said that he had had several slight ones, but I could observe nothing except that after some of them there seemed a little longer interval in the heart-beats, and then two or three closer together. The pulse at the wrist was from 29 to 31, mostly regular, of good force and tension. The arteries appeared smooth and elastic at the wrist and the temple. The impulse was not exaggerated nor the dulness increased. There was a strong double beat (the normal sounds) synchronous with the radial pulse. Between them one faint beat, which sometimes seemed to be more developed, so that the pulse was apparently quicker, but this was not frequent enough to greatly increase the number of beats per minute. There was a systolic murmur, loudest at the base. This examination was made without a stethoscope. Through the courtesy of the patient and Dr. Edson I had the opportunity of examining him again last March—that is, about a year and a half after the first examination. Dr. Edson informed me in his note that "for a year his pulse has kept at 28 and is full and perfectly regular, with none of the faltering it showed when you saw him. His lapses of consciousness grew less frequent until May last, since which date he has had none." I found that he had not only had

at a time when the patient was still going into town to attend to his business, alternations of heavy or difficult breathing, with pauses of apnea lasting several seconds, evidently Cheyne-Stokes, or something very much like it, occurring at night.

no losses of consciousness, but not even any faintness or dyspnea unless on going up stairs too fast. He walks out, and even cuts a little wood. He is somewhat deaf, varying at times, but always the most on the right side, where there is a slight trace of facial paralysis. I examined his heart with the phonendoscope, but through his clothing, and thought that I could at times make out a lesser beat after the principal one.

TRACING 3.[1]



A pulse considerably below the average is much more likely to call the attention of the physician and the patient than one above it, as being much less common and less easily accounted for by any of the usual conditions which raise it—exercise, nervous excitement, and especially fever. The fact that so many cases of it have been reported shows, indeed, that it strikes the practitioner as an unusual circumstance. The statement of Gossett Brown,[2] however. who says that in many thousands of cases in both hospital and private practice he had seen two cases of slow pulse, is a somewhat extreme one. He evidently refers to the remarkably or phenomenally slow pulse of which both of his cases are instances.

Riegel,[3] taking 60 as the figure of the normal pulse, finds among 4484 men and 3083 women, 710 and 331 cases of slow pulse respectively, a total of 1041 in 7567; but of all these, he says, only 47 were connected with diseases of the organs of circulation.

What is to be regarded as a slow pulse? An average of a large number of promiscuous counts would have little value, and the variations depending upon age, sex, position, etc., have been sufficiently often stated. A very interesting statement was made by Gros[4] in regard to the Bretons whom he had the opportunity to observe in the military hospitals during the Franco-Prussian war. They had habitually their pulses considerably below the average of the rest of

[1] The tremor in the upper tracing is an instrumental error. The lower line is taken simultaneously with the upper, with a shorter lever. It may be read with a cylindric lens. See TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, vol. xv. p. 270.

[2] Brit. Med. Journ., December 27, 1879.

[3] Zeitschr. klin. Med., 1890, p. 221.

[4] Union Méd., Paris, 1870, p. 658.

France. I have seen a similar statement as to the Central African negroes, but I do not know on what original authority.

Riegel quotes Kaiser as saying that whole families show slow pulse. Russell[1] reports the case mentioned to him by Crompton, of a man whose pulse had been notably slow for years, but who has long been an enthusiastic salmon fisherman and sportsman. His son has also a very slow pulse.

For the sake of round numbers we may call 60 the lower limit of the usual normal range, which would probably be little if at all below the correct figure for the greater number of large, strong, and healthy males. The upper limit, which would apply more closely to smaller, more excitable, and active persons and to females, might be put in the neighborhood of 80.

It is usual to report cases of a pulse considerably below this as being found in perfectly healthy persons. There are a few in which it is impossible to dispute this diagnosis, but there are others more numerous, in which careful inquiry or the course of time shows the condition of alleged health to be subject to serious exceptions. In fact, such cases are treated of by Huchard as a separate class of Stokes-Adams disease.

It is customary here to speak of Napoleon I., who is said to have had a pulse of 40, and to have been uncomfortable when it rose to 60. Various authors state different figures, but for the sake of emphasis I mention the lowest. According to Ogle (*Lancet*, January 26, 1897[2]), who made careful inquiries, there is no record of this pulse, but it is a tradition resting upon the verbal statements of Corvisart.

Dr. O'Meara, Napoleon's physician at St. Helena, records, however, that his circulation was very feeble, rarely exceeding 58 or 60 in a minute, and most frequently was 54. The strange thing is to find this spoken of as a normal condition in face of that other tradition resting on the same basis, but scouted by many Frenchmen, of epilepsy, and of the facts recorded by many historic writers of those strange attacks of depression and apathy, lasting for some hours, which assailed him on more than one critical occasion. Is it not

[1] Medical Times and Gazette, 1877, p. 229.

[2] It is more than forty-five years since Dr. Ogle's early communications on the subject of slow pulse appeared.

quite as reasonable, as Ogle suggests, to unite the two symptoms into the well-known group of the permanent slow pulse with syncopal or epileptiform seizures?[1]

Cases of physiologic slow pulse are not common. Some which are so designated would be more correctly described as cases which up to the time of report would not have shown any other obvious symptoms.

Mr. Mayo[2] describes several which are certainly open to but little criticism, even if classed as physiologic, but which are prudently called by him "compatible either with ordinary length of days, or, at all events, with the continuance of life for an indefinite period."

The first was that of a man, aged thirty-five years, rather delicate, whose pulse for many years was about 40, regular, full, and strong. The action of the heart was healthy. He was in perfect health and supposed himself to be as capable of bodily exertion as other persons of the same slight frame as himself.

The next was a clergyman who died at thirty-two years of age of obstruction of the bowels. He was exceedingly active in mind and body. Hills did not embarrass his breathing in the slightest degree. He frequently, however, like most other excitable persons, had fits of languor and depression. His pulse was regular at 36. When the body was examined, commencing ossification of the aortic valves was found.

In his third case there seemed to have been no connection between the slow pulse and some not very severe ailments. The patient occasionally rode eight miles to market.

Vigouroux[3] stated that he had known for five years a laborer whose pulse and heart always beat at the rate of 20. During this time he never attended him but once, and then for "embarras gastrique." On the day of writing he had seen him in hot weather driving a cart with six oxen, "an exercise which demands a certain amount of health and energy."

There are a very few cases in which an acquired slow pulse seems to have become distinctly physiologic. This is difficult to understand unless we admit that the healthy heart is capable of doing an amount

[1] Dorsey Gardner, Quatre Bras, Ligny, and Waterloo, 2d ed., pp. 34–36.
[2] London Medical Gazette, N. S., vol. xxii. p. 282.
[3] Gaz. des Hôp., 1876, p. 788.

of work greatly in excess of what it is ordinarily called upon to do; that is, that the margin is a very wide one and that the physiologic estimates of the amount of blood pumped by the heart are maximums which very much more than cover the ordinary and necessary work. There is perhaps in such cases some adjustment of the capacity and elasticity of arteries, making in effect a larger reservoir, so that an extremely slow pulse may give a stream sufficiently steady for practical purposes. The case of Dr. Archibald Hewan is an interesting one. His pulse, from overstudy and from gout and rheumatism, gradually fell from 72 to 38, where it remained, but he never had a fainting fit. He was able to climb a mountain some thousands of feet high, his pulse at the top being 40.

Before discussing the mechanism and causes of slow pulse, it is well to mention briefly the principal clinical conditions under which it has been met with. Beside the somewhat doubtful physiologic class, we find it in convalescence from acute diseases, and in the course of some acute diseases, especially acute rheumatism.

Atkinson[1] remarks: "It is evident that bradycardia occurring in acute rheumatism cannot in all cases be considered with the phenomena of convalescence from acute febrile disease as some are disposed to do."

Schuster[2] reports the following: "A child of four years went through with articular rheumatism with no indication of heart trouble, but after the acute symptoms had passed and the pulse was of normal frequency, a strong systolic murmur was heard at the apex. When this also was in the way of improvement a series of attacks were developed, coming on in the evening after the child had been asleep, in which the pulse, which had been small and arhythmic, gradually decreased in frequency, together with the temperature and the respiration, which latter also took on the Cheyne-Stokes type. The next morning the child would wake up feeling pretty well. This lasted three weeks, when improvement began and continued until an attack of herpes zoster, when there was a new series. Later still, after renewed improvement, there was a third series, less severe and coming in the morning. In a later attack of measles there was no heart disturbance.

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1891, and Virginia Medical Monthly, December, 1891.

[2] Deutsch med. Wochenschrift, 1896, p. 484.

The slow pulse of the puerperal condition is probably of the same character. In none of these conditions is it usually extreme or long-continued. In convalescence it usually occurs with a slight fall of temperature below the normal, and is simply a part of the general reaction from the fever. Examinations of considerable numbers of puerperal cases seem to show that while the slow pulse under these circumstances has no unfavorable significance it cannot be called exactly physiologic, inasmuch as it is not invariable, nor in the majority of cases well marked. Heil,[1] Labousquière,[2] Grüneisen,[3] Varnier.[4]

A large number of poisons, both vegetable and autogenetic, have a marked influence upon the rhythm of the heart. Among these are, of course, digitalis and its congeners, which slow the beats through their excitant action upon the vagus and vasomotor centers, the solanaceous alkaloids which act in the opposite direction by an opposing mechanism, and a considerable number which seem to have a general depressing effect upon the whole cardiac motor mechanism, such as aconite, saponin, muscarin, colchicum, and others. The position of tobacco is interesting and peculiar. It seems sometimes to be the cause of temporary slow pulse, although this is likely to be changed to a very rapid one by a slight exertion, but it has nothing to do with the etiology of the permanent slow pulse. Several of the most typical cases have had nothing to do with tobacco, and in others it has not been used to excess. My friend Dr. Starbird, the surgeon of the Soldiers' Home at Chelsea, where the principal employment of several hundred inmates is the consumption of tobacco, has for some years been looking in vain for a case of permanent slow pulse to show me.

Peaslee[5] speaks of two cases of slow pulse, both attended with occipital pain, which recovered at once on discontinuing the weed. He recalls the fact that when examining recruits during the war he found many young men with slow pulse who turned out to be cigarmakers. He mentions also, which is interesting as showing the power of psychic action on the rate of the pulse, and also as speaking well for the courage and patriotism of the expectant soldiers, that the pulse invariably rose when they were informed that they were accepted.

[1] Arch. f. Gynäkol., 1898, p. 265.
[2] Ann. de Gynecol. et d'obstétrique.
[3] Halle, A. S. Thesis, 1898.
[4] Ann. de Gynecol. et d'obstét., 1899, p. 30.
[5] New York Medical Journal, vol. xxiii.

Tanquerel des Planches (*Lead Diseases*) states that in 1217 cases of lead colic observed by him, 678 had a pulse of from 30 to 60.

Whether the pulse follows the temperature, as it does to some extent *below* the normal, although much more decidedly upward, on account of a direct action or because some special toxin is formed, is not easy to say; there are reasons for supposing the former. The relation of temperature to the rapidity of rhythmic action is interestingly shown by the chirping of the tree cricket, which follows very closely, as was first pointed out by Professor Dolbeare,[1] the temperature of the atmosphere at the rate of four chirps to the degree Fahrenheit.

In some physiologic experiments where the heart is cut off as completely as possible from all other influences, one may find a relation between pulse and temperature almost as close as this, but only in a few instances of the human heart does its beat follow the thermometer so closely and accurately.[2] The analogy, however, between the slow and disconsolate chirp of the cricket when "the melancholy days have come" and the reluctant pulse of bradycardia is a striking one, even if not scientifically valuable.

The following case is of more interest as showing some intimate relation or close neighborhood between the pulse regulating and heat regulating centers, a dependence of pulse on temperature:

Nieden[3] records the case of a man who fell down stairs in such a way as to strike against a wall at the bottom with his outstretched arms, dislocating, as it afterward was found, the first dorsal vertebra without fracture, but compression of the cord. There was a complete paralysis of the lower extremities, the chest, and the greater part of the trunk. There was then progressive lowering of the temperature and pulse, consciousness remaining perfect to the time when the pulse was 30 and the temperature 81°. Death took place on the eleventh day with a temperature of 80.6°. The most remarkable circumstance about this case, in addition to its furnishing the lowest recorded temperature, is that there should have been any fall of temperature at all, for although a fall of pulse is usual, or at least very common in fractures of the cervical portion of the spine with injury to the cord (see Table

[1] American Naturalist, 1897, p. 970, and 1899, p. 935.
[2] Journal of the Boston Society of the Medical Sciences, November 21, 1899, p. 89.
[3] Transactions of the Clinical Society, London, vol. vi. p. 75.

II.), the rule is exactly the opposite as regards temperature, which rises, often to excess.

Williams and Arnold found in young men, after long and severe exercise[1] that there was a fall of temperature and of tension as shown by the sphygmograph, but a very rapid pulse.

Handfield Jones[2] gave belladonna in a case of low pulse and temperature without effect upon the pulse, but raising the temperature some degrees.

In many cases of bradycardia the temperature is a degree or two below the normal, and this condition is not infrequently accompanied by a subjective sensation of cold.

The combination of a subnormal temperature and a pulse which, if not pathologically slow, is close to the lower limit or normal, seems to be met with in persons who are not absolutely sick, but who are not strong, get easily tired and do not recover rapidly from acute illness.

The pathologically slow pulse seems not infrequently to arise from extreme muscular exertion or strain, and even in some cases emotional depression. This effect may be a temporary one or more frequently passing off after a few days, although some cases of the permanent form trace their origin to conditions of this kind.

Observations of very slow pulse have always excited the attention of physicians, and the number of recorded cases is very considerable. Taking out the well-defined classes which have been spoken of, the remainder still consists of the most interesting and important. I have made a collection of all that I could find presenting a certain train of symptoms and tabulated them on that clinical basis before attempting to attach to them definite pathologic conditions. Those in which a postmortem examination was made are in the first table. The first and most important group of recorded cases consists of those of the so-called Stokes-Adams disease or permanent slow pulse with acute exacerbations, attended by vertiginous, syncopal, epileptiform or apoplectiform attacks.

If the names of discoverers or of those who have been the first to describe special diseases are to be attached to them they certainly should be to what they have described and not to a theoretic patho-

[1] Marathon Runners. Transactions of the American Climatological Association, 1899.
[2] Lancet, December 30, 1876.

logic condition. Adams and Stokes both described cases exhibiting the group of symptoms which I have taken as a basis for the table. There are modifications which are undoubtedly closely allied to, and which throw much light on, the typical form, in which certain of the phenomena have not reached the same completeness as the others, and, again, it is not only possible but almost certain that this larger symptomatic group must be broken up on the basis of pathology into smaller ones, though for all this it must be admitted that it is as a whole well-characterized and distinctly limited.

In these cases, on the occasion, perhaps, of a sudden attack, an early one of those which later characterize the disease, or perhaps by accident, a pulse is found which is very much below the average in frequency. On recovery it rises in frequency more or less, but still remaining below the average. The figures vary a great deal. In the table the larger numbers in the third column apply chiefly to the usual condition—that is, between the exacerbations or fits—and the very small ones to severe attacks. The habitual pulse varies considerably from day to day, and has been given in detail in some of the reports, which I did not think it worth while to reproduce, as the very slow pulse is subject to some of the same influences which change the rate of the normal one. The range of frequency may be seen in the tables. It has been noted, however, in some cases, that posture does not alter the rate so much as in health. Fever, however, increases the rate as in normal conditions. In the case of Mrs. P. (Case I.) the pulse is, for the sake of brevity, given only during several periods of a few days each. In the first, it may be seen that a decided drop in the pulse coincided with a moderate fall of temperature. Whether this was the initial fall I have been unable to ascertain. During the paroxysms the heart may come to an absolute standstill, lasting for as much as a minute, and it may be as low as 4 per minute for several successive minutes; 6 per minute has been counted for an hour.[1]

The failure of the heart has been observed to precede the nervous symptoms, so that the physician with his finger upon the pulse has been able to predict the onset. An aura of various kinds has been observed in many cases.

Rhythm. Many writers have cautioned against the error of mis-

[1] Kinkead. Dublin Journal of the Medical Sciences, 1898, p. 4.

taking a slow pulse for a slow beat of the heart, and object on this ground to the use of the word "bradycardia" to describe an infrequent radial pulse. One author goes so far as to make this error cover most of the cases of the class we are considering. While it is, of course, true that such an error may be made, I have not found, in reading over a good many cases, that it often has been; many authors stating that the heart-beats were synchronous with the radial pulse, and others showing by implication that they were aware of the possibility of error and avoided it. Beside this, it seems from what follows that the error, if it be one, does not materially affect the pathology.

There are certain transition stages between the ordinary rapidity of the pulse and the phenomenally infrequent one which are very interesting. It is well in noticing the various changes in rhythm to take as a starting-point the slow pulse in which no sign of interpolated beat can be in any way detected, either at the wrist or at the heart. Such a pulse is usually of fair strength, so as to be very distinctly felt and heard. The slowness, or, to be strictly accurate, the infrequency, consists not in a general prolongation or proportional drawing out of all the elements of the cardiac cycle, but of a systole as sharp and decisive as the normal, and a great prolongation of the diastole. That there is no prolongation of the systole it would be hard to say, but it is very evident from sphygmograms that it is not prolonged in proportion to the diastole. A physiologic writer, to whom I regret that I cannot now give a more exact reference, has stated that the systole of the normal heart beat varies in proportion of the square root of the diastole, and most of the sphygmograms look as if they conformed quite nearly to such a ratio. Garrod, however,[1] says "the length of the interval between commencement of the primary and dicrotic rises is constant for any given pulse-rate, and varies as the cube root of the pulse-rate." Thurston[2] confirms this.

For the proofs of this general statement without mathematic accuracy, I may adduce the observations of many auscultators and many sphygmograms. Those taken in Prentiss' case and published in the fourth volume of our reports are very characteristic. I have taken others of a similar form in several cases, and they are to be found in the literature, nearly all bearing the same marks of an ener-

[1] Proc. Royal Soc., 1870, p. 351, and 1875, p. 142.
[2] Journal of Anatomy and Physiology, 1876, vol. x. p. 497.

getic upstroke (systole) often a plateau of rest, although this is certainly much more marked in some than in others, and a quite rapid decline without a trace of dicrotism until the level is reached just before the next pulse. When the pulse is very slow[1] the pressure may have reached almost to its minimum some time before the next stroke. In the middle pulse of the second sphygmogram on the page mentioned the descent during the last one-third of the diastolic interval is extremely small.

There are sphygmograms which represent a much more gradual rise in the obliquity of the upstroke, but there is a possibility of instrumental error.

A unique observation is that of Auché and Martin,[2] who examined a man who was subject to attacks of vertigo and who had habitually a pulse of about 40, by means of the radioscope. They say "the cardiac contraction is brisk and does not last longer than ordinary. Dilatation is rapid, but when it is accomplished the heart rests. During the whole of the long pause ('grand silence') it is impossible to determine the least contraction or auricles or ventricles. There is no abortive systole."

On some sphygmograms interpolated beats may be distinctly marked, which from their character and position seem to correspond to ventricular contractions. In a paper by Dr. Putnam,[3] not upon this subject but upon the pulsus bigeminus and trigeminus, sphygmograms are given where three successive beats grow less and less, so that if such a pulse had been counted only by the strongest pulsations it would have been at the radial only one-third of its true number at the heart.

The occurrence of abortive beats has been long recognized in connection with disease of the heart other than that we are considering, especially in mitral stenosis, where it is not difficult to account for on mechanical principles. The dropping out of beats appears to be one method of formation of the slow pulse from the normal, the intermediate stages having been observed, as if the heart declined to continue a useless labor, but it is not certain that it is the only one. If such intermediate stages have existed in all cases they have certainly not

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1889, p. 122.
[2] Gaz. Hebd., 1898, p. 87.
[3] New York Medical Journal, September, 1874.

been observed. Baumgarten[1] mentions the case of a young man dying of diphtheritic paralysis of the heart, where the development of a slow pulse of 25 from a frequent and irregular one was traced as occurring in this way. He goes on to remark that "the very rare pulse of atheroma of the coronary arteries—never *quite* regular—is undoubtedly of this character." I should doubt if it were always developed in this way, although from the rarity of cases in which the development has been watched from the beginning, and also from the possibilities of coronary disease existing beyond the limits usually examined, it would be impossible to disprove it from recorded cases. An interesting converse may be found in the action of digitalis. Under the influence of this drug stimulating the vagus, the heart-beats become gradually slower and the tension rises. When overdoses are given and poisoning takes place lesser beats are interpolated, and finally a rapid pulse is established.

It does not appear that in the slow pulse at any period of its development, nor in the recovery from this condition, which has been sometimes sudden and sometimes gradual, the interpolated ventricular beats are an essential feature, although they may occur at any stage.

Another set of intermediate pulsations observed at the heart, and sometimes in the jugulars, but not at the radials, seems to be quite clearly shown to depend upon contractions of the auricles which go no further, and are not, as in the normal condition, followed by contraction of the ventricles. Pouzin[2] refers the sound to the closure of the auriculoventricular valves, which are heard separately instead of being merged in the other missing elements of the first sound. They thus mark the time at which a systole should occur, but does not. Bristowe[3] observed a motion imparted to the stethoscope placed near the base of the heart which was wholly unattended by cardiac sound or pulsation in the arteries.

The tracing of cardiac, radial, carotid, and jugular pulsations taken by Vaquez and Bureau,[4] in a case of slow pulse with cardiac sounds not corresponding to anything at the wrist, but attended with jugular pulse, as well as those of Chauveau,[5] seems to put the occasional existence and proper explanation of such purely auricular pulsations beyond a doubt.

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1888, p. 236.
[2] Thèse de Paris, 1898.
[3] Lancet, March, 1885.
[4] Mém. Soc. de Biol., 1893, p. 170.
[5] Rev. de Méd., 1885, and Lyon Médical, 1883.

Whether the change from the usual to the slow pulse takes place by the dropping of beats, first a partial failure of the ventricular, then the total, and at last of the auricular, is not certain. Comparatively few cases have been observed in their formative stage, but in some it has appeared that this succession has been observed. In others, however, there is no reason to suppose that a simple elongation of the interval should not have occurred, just as happens when a very frequent febrile pulse drops down to normal.

In many cases the first observations made, some of them at an early stage, make no mention of intermediate weak beats.

The nervous symptoms of the paroxysms vary a good deal in form and severity. They do not always preserve the same type even throughout the same case, varying from simple vertigo to complete loss of consciousness, with convulsions. In a few cases they have been described as epileptic instead of epileptiform, and in others—notably the original one of Adams, as "apoplectiform," with the remark that they are not followed by paralysis. Different forms do not seem to be attached to any special train of cardiac symptoms or cardiac conditions, nor can the prognosis be very accurately based upon them, as there have been instances of permanent slow pulse where the only representatives of the paroxysms, although genuine, have been so slight as to attract little attention, and yet the patient has died suddenly in another.

Dyspnea accompanies many attacks, but is not so invariable a symptom as we should expect when the cardiac function is so extremely depressed. The respiration, except, of course, in the cases where convulsions take place, is more likely to be quickened than slowed to correspond with the heart.

The paleness of the face which ushers in the attack has been mentioned in many histories.

The number of cases which I have included in the first table on the basis of the symptoms and in which an autopsy has been made is thirty-four.

Naturally the records vary widely in completeness and possibly also in trustworthiness, but in very few of them has there been any satisfactory examination of what we cannot help regarding as a very important if not essential point, that is the nervous supply of the heart, especially the sympathetic cords and the intrinsic ganglia of the heart.

To anyone who has sought for the ganglia among the cardiac plexuses and in the heart itself it is not necessary to suggest a reason why they have not been more frequently examined with modern histologic methods. Whether the fate of Dr. Robert Lee, who got into much trouble with the Royal Society for his too abundant discoveries of ganglionic nerves, has had any discouraging effect on would-be investigators may well be doubted. In our more liberal times anatomic results rather than ethical obstacles have probably been more effectual in keeping these structures out of the routine of the ordinary postmortem, and as typical cases are among the rarities of clinical observations, the chances of the right case falling into the hands of the zealous histologist are small. These structures are far from easy to find except by the tedious process of embedding and cutting of serial sections from the regions where they are likely to be found, and many sections may be examined without finding any.

They are situated in the septum of the auricles in the triangular space bounded on each side by the diverging walls of muscle, and above by the pericardium, immediately beneath which latter they lie, being specially grouped above the foramen ovale, and more posteriorly where the septum comes down to the sulcus between the auricles and ventricles. They are said to extend beyond these regions, especially along the sulcus, and probably do so in a scattered way, but practically these are the best localities to search. They are not to be found at all below the transverse sulcus in man, but are described by some authors[1] as occurring over the upper third or two-thirds of the ventricle in some animals. For examination in the fresh condition they may be found by dissecting out from the appropriate localities pieces of nerve and tearing them apart with needles. This is not a very certain method, as many pieces may be examined without success, but occasionally one may get in this way a very satisfactory specimen. I have once in a very emaciated heart found just beneath the pericardium, lying over the top of the auricle, a couple of small ganglia the size of very small pinheads.

The structure of these ganglia is that of sympathetic ganglia in general, consisting of from one (on section) cell to forty or fifty or more with fibers of both kinds, white and gray. The cells are en-

[1] Kazem-Beck. Cbl. f. med. Wiss., 1897. Jacques: Journal de l'Anat. et de la Physiologie, 1899, vol. xxx. p. 633.

closed each in its capsule, consisting of many small nucleated cells. The nerve cells have a very finely granular or rather semiopaque parenchyma less pigmented than that of many sympathetic ganglia, and a large nucleus. The ganglia resist with considerable tenacity the process of dilaceration. These ganglia have been investigated by a considerable number of histologists in various diseases, but among them there have been few, if any, cases of the kind we are considering. They are as follows: Romberg and His:[1] Embryologic. Cardiac ganglia are offshoots from the sympathetic and remain connected with it; hence can be only sensitive.

Dogiel:[2] Anatomical.

Schwarz[3] showed specimens of ganglia. They are few in the mammalian heart, situated superficially in and above the auriculoventricular sulcus. They lie mostly in the neighborhood of the mitral valve. They should not be confounded with the "mast cells," which are found all over the surface of the ventricles and which have given rise to some of the mistakes.

Lübimoff:[4] Histology; many drawings. Pathologic changes consist in thickening and degeneration of the cell capsules. Thickening amyloid degeneration, and metastases (micrococci) in the vessels, and degenerative changes in the nerve cells. The latter in adults always contain pigment.

Ivanowsky, *Rudneff's Journal* (Russian)—abstract from Putjatin (v. i.): Observations on spotted typhus. Changes chiefly parenchymatous, but capsular endothelium often swollen. He explains by these changes the heart paralysis which caused death in the early periods of typhus.

Putjatin[5] examined ganglia in three groups of cases. In the first two groups there were serious organic changes in the heart. In the third the changes were dependent on constitutional disturbances. Fibrous intergrowth in ganglia. Degenerative changes in protoplasm.

Uskow:[6] Changes in the heart ganglia connected with hypertrophy of muscle. Chiefly in the medullated fibers, which lose their myelin sheaths and show the process of proliferation of the nuclei. The visible changes in cells are limited to thickening of their capsules with

[1] Prager med. Wochenschrift, 1890, p. 331.
[2] Arch. Mikr. Anat., xv. and xx.
[3] Berl. klin. Woch., 1898.
[4] Virch. Arch., lxi. p. 145.
[5] Ibid., lxxiv. p. 461.
[6] Ibid., xci. p. 453.

proliferation of the capsular nuclei. If certain acute diseases occur the changes pass on to parenchymatous inflammation. In two children with diphtheria he found no changes.

Kusnezow:[1] Changes in acute and chronic endocarditis. In acute endarteritis disease of the ganglia is observed in the form of inflammatory granulation formation, increase and swelling of capsule—endothelium, and albuminoid and fatty degeneration of the nerve cells themselves. The changes of the ganglia situated in the lower part of the auricular septum depend for the most part on a spread of the granulation process by continuity from the valves to the fatty tissue surrounding the ganglia. Pigment changes are not always physiologic. Changes in the muscle substance do not stand in most cases in direct relation to the changes in the ganglia. It is only in rare cases that it is possible to determine in a pathologic-anatomic way the dependence of alterations in the activity of the heart upon diseases of the heart ganglia.

Winogradoff:[2] Degeneration of nervous ganglia of heart after chloroform poisoning. Granular degeneration. Changes in the automotor heart ganglia in hereditary syphilis. Especially marked in the interstitial stroma of ganglia and accompanied by changes in the vessels and the connective tissue surrounding ganglia. Changes of ganglia in pneumonia.

Wassilieff:[3] Changes in heart ganglia in lyssa. Shrinkage in capsules from edema.

Ott:[4] There are no ganglia in or upon ventricle. They are in the septum of the auricles and also in circumference of auricles, their number diminishing as distance from septum increases. They are especially found in subpericardial connective tissue, but some are found embedded in muscular substance.

Two types of alteration. First, development of connective tissue substances (progressive), met with under conditions which lead to congestion and changes of size in the heart.

Second, changes in the nerve cells (regressive) found in cases with more deeply acting qualitative alterations of blood (parenchymatous). Thirty-two cases were examined, in nearly all of which some form of

[1] Virch. Archiv, p. 132, p. I.
[2] Cbl. f. Chir., 1884, p. 847. St. Pet. med. Woch., Beilage, p. 54. Wien. Med. Presse, 1886, No. 6.
[3] Cbl. f. med. Wiss., 1876, p. 785.
[4] Zeitschr. f. Heilkunde, 1888, p. 271.

heart disease was present, but among them no cases of very slow pulse. In most of them, where the clinical phenomena are noted at all, the pulse was rapid and frequently irregular. In a single one it is noted as slow and rhythmic. This was a case of chronic endocarditis, with chronic Bright's, etc. The heart was pale and flabby. There was increase and swelling of nuclei of the sheath of Schwann, also of round interstitial cells. There were many ganglion cells which appeared as if compressed by the sheath (im Schwinden begriffen). The protoplasm was finely granular. In some cells the nuclei were still visible, in others not.

In four cases where the degenerative changes in the nerve cells were very marked the pulse had been noted as follows:

Tuberculosis, and many other lesions; pulse frequent, strong, rhythmic.

Pneumonia; alcoholism; pulse frequent, strong, rhythmic.

Acute atrophy of liver; pulse frequent, weak, rhythmic.

Phosphorus poisoning; pulse frequent, weak, rhythmic.

The paper of Eisenlohr I have not seen, but judging from many references to it his results are much like those of Ott.

The two balancing systems of nerves which regulate the beat of the heart take their origin in the medulla oblongata, and although in a manner functionally opposed, their centers are probably quite near to each other.[1]

From this region they take different routes, that of the regulatory or inhibitory passing directly in the vagus to the cardiac plexus, and the accelerator or augmentor principally down the cervical cord to its lower portion, where it unites with the stellate ganglion formed by the union of the last cervical and first dorsal sympathetic ganglia, which in turn sends branches to the cardiac plexus. After the cardiac plexus is formed by the union of the two nerves on each side, joined by some smaller filaments from the upper ganglia, it is impossible to say from what source any special bundle is derived. The cardiac plexuses are united with the intrinsic ganglia of the heart situated as already described, breaking up into smaller and smaller branches, and are distributed plentifully over the heart muscle.

Anatomically the heart muscle agrees neither with the smooth nor with the voluntary muscular fiber, and physiologically stands between

[1] Porter, in American System of Physiology, 2d edition, p. 177.

them. Although having striæ like the voluntary muscle, a structural condition undoubtedly connected with its capacity, or rather necessity, for rapid contraction, yet it may contract, not only many times but rhythmically, without any new stimulus from the nervous centers, and, so far as can be seen, without assistance from nerve cells and perhaps even without any nervous fibers.

As the heart is simply a portion of a hollow tube surrounded by muscle for the purpose of propelling the fluid contents to the next segment beyond, each of its beats may be looked upon as the analogue of a limited peristaltic wave, such as propels the contents of the intestinal canal, the ureters, or the uterus, but differing from these in the very essential point of rapidity of propagation.

It is very probable that the intrinsic ganglia are to be looked upon not as exactly automotor, in the sense of initiating independently the cardiac cycle, as has been assumed by many writers; nor, on the other hand, as exclusively sensitive, as it is urged upon embryologic grounds they should be; but reflex centers controlling the proper succession of impulses.

They are thus akin to the local regulatory centers connected with various organs like the ophthalmic ganglion with the iris, but more especially to the plexuses of Meissner and Auerbach in the intestinal walls.

Although it has been conclusively shown that the muscle of the ventricle does not require a nervous impulse from the auricle in order to contract and even to beat rhythmically, yet the nerves passing from the cardiac plexuses over the auricle and through its ganglia to the ventricle are necessary for the proper correlation of their beats and making their contractions effective in propulsion instead of disorderly and confused.

These small ganglionic centers to which the nerve fibers of the auricles and ventricles stand in the relation of afferent and efferent conductors are under the control of both the vagus and the sympathetic, the latter perhaps supplying a constant portion of potential energy, or, in other words, keeping up their reflex tone and the vagus controlling its discharge and regulating the intervals at which it shall take place.

In Table I., containing the cases which present the typical Stokes-Adams symptom group during life, and which were examined post-

mortem, there are to be found three (Nos. 4, 9, 31) where a distinct lesion of the bulb or the cervical portion of the cord was found, or four, including the horse (34*a*).

King[1] states that a lesion in this region is the "only known cause of slow pulse," and brings forward a considerable number of cases where a slow pulse was connected with such a lesion (Table II.), most of which, however, were not subject to the exacerbations which mark the type. He admits, however, that there are other possible causes.

We can say, as to brain lesions, that intracranial pressure frequently produces a certain amount of lowering of the pulse-rate, but seldom of an extreme degree, and also according to Mr. Hutchinson, irregularity. This kind of slow pulse may arise from lesions differing in kind and position, but probably all producing ultimately a pressure on the bulb.

Table II. makes no pretence to completeness, and it could undoubtedly be considerably extended by a reference to surgical records of injuries to the cervical vertebræ as well as to medical reports.

The objections to considering the permanent slow pulse, whether existing as a single symptom or making a part of Stokes-Adams disease, to be dependent upon the irritative lesion involving the origin of the vagus or of its inhibitory fibers are the following:

A constant irritation rarely lasts so long and with so little change in character as happens in these cases. Some paralyzing degenerative lesion is much more naturally looked for.

In health the pneumogastric's function is to hold down the pulse within certain limits, in order to secure the most advantageous rate of expenditure. It is a sort of check upon and not an opponent to the activity of the augmentor nerves. In experiments upon mammalians it is never possible to hold down the pulse for any length of time by stimulating the vagus. After a short pause the heart begins to beat again slowly, and then resumes its usual rate, or assumes a new regular rate, even while the stimulation of the vagus is still going on.

The alkaloid atropin is known to paralyze the inhibitory function of the vagus from one end to the other. If atropin is given in a case of slow pulse dependent upon intracranial lesions irritating the vagus, it quickens the pulse materially, but in the cases of permanent slow pulse it produces at most only a very slight effect or none at all.[2]

[1] Lancet, 1845, vol. ii.

[1] Dehio. St. Petersburg med. Woch , 1892, No. 1.

It is singular that this well-known property of atropin should not have been utilized for diagnosis before. Atropin and belladonna are recorded as having been used in a considerable number of cases without benefit, but the special diagnostic significance of this seems to have been overlooked.

A lesion in the course of the vagus was found in one case (No. 8), and possibly in No. 1.

In Case 14 the authors consider the degenerative vascular changes in the brain, which they found most marked in the cerebellum, to be the most important. It will be seen by noting the condition of the brain found in many other cases that, leaving out of consideration the general atheroma which is so frequently found when no definite symptoms or varying symptoms of all kinds have been present, and which (the atheroma) may or may not have involved the nutrient arteries of the bulb, we have nothing by which to connect any special intracranial lesion with the rapidity of the pulse.

Taking the four cases of Table I. with the larger number of Table II., some of which are very clear and distinct, we find little to sustain the theory that the permanent slow pulse is the consequence of an irritative lesion of the bulb, but there appears a very evident connection with a lesion of the cord lower down—*i. e.*, from just below the bulb down to the first dorsal vertebra, as has been clearly pointed out by Charcot.[1] A narrowing of the canal at the occipital foramen affects the cord rather than the oblongata. The cases I have quoted are lacking in a minute description of the histologic changes, but it is evident in many of them, from the absolute paralysis of sensation and motion, that all fibers were thoroughly involved. The lesion was in all cases situated above the point where the augmentor fibers leave the cord to join the compound or stellate ganglion on their way to the heart. There can certainly be but little doubt of the existence of one group of cases dependent upon a paralyzing lesion of the augmentor nerve-poles within the cord.

Lesions of the stellate cervicodorsal ganglia have not been observed in such cases, but these ganglia have been very seldom examined.

Fränkel[2] reports a case in which he found them seated in small abscesses connected with a limited pleurisy, but the symptoms were not such as to have any bearing on our subject, being largely of a

[1] Système Nerveux, Sér. ii. p. 135.

[2] New York Medical Record, June 16, 1900.

hysteric character. In Prentiss' case I examined them, but found nothing characteristic.

Hutchinson[1] says that when there is a fracture of the spinal column high up the pulse diminishes in frequency and is remarkably large and full, and remarks upon the peculiar impression made by a man screaming with pain and a countenance expressive of the utmost suffering and anxiety, but whose pulse was slow, full, and deliberate—48 in the minute.

The cases remaining in the table may be distributed as follows, with reference to the cardiac and vascular lesions:

CLASS I.—Pericarditis. Cases 5, 32.

CLASS II.—*Group* 1. Valvular lesions and simple dilatation. Cases, 24, 25, 26, 27, 28, 30, 31, 32.

Group 2. Atheroma of aorta and general. Cases 3, 6, 7, 12, 14, 15, 17, 18, 20, 22, 23, 24, 25, 28, 29, 30, 33.

Group 3. Atheroma of coronaries. Cases 3, 12, 18, 21, 24, 27, 29, 30.

Group 4. Degenerative change of the muscles. *a*. Fatty. Cases 6, 13, 16, 17 (?), 18, 21, 22, 24, 26, 29, 30 (?), 33, 34. *b*. Fibroid. Cases 19, 20, 29, 32.

Group 5. Degenerative changes of ganglia. Cases 6, 32.

CLASS III.—Nothing decisive. Cases 1, 2, 7, 10, 11.

In Case 1 neither the aorta nor coronary arteries were atheromatous. The heart was rather large and firm.

In Case 7 the coronary arteries were normal. The aorta was smooth, except a few small plaques of atheroma in the beginning of the thoracic and above bifurcation.

In Case 10 the results were completely negative.

In Case 11 the arteries were remarkably free from atheroma and the coronaries pervious.

The connection of slow pulse with general arteriosclerosis is an interesting and important but far from invariable one. A greater or less amount of atheroma, in several being so slight as to have practically no effect, was found in nearly half the cases in my table, but it is well known that by far the greater number of cases of arterial disease are attended by no such symptoms.

The same things are true of the muscular degenerations, espe-

[1] London Hospital Report, vol. iii. p. 366.

cially the fatty, of which the more common symptom is rapidity and irregularity. The fatty heart of which Kisch[1] makes the slow pulse a rather common symptom is that which is a part of general corpulence and has little to do with paroxysmal bradycardia. It is only dangerous when permanently down to 50 or 30, which is very rare.

Much weight has been laid upon degeneration of the coronaries, first as a known cause of the muscular lesions, and secondly as a possible cause of a possible ganglionic lesion. It is recorded in eight of the thirty-four cases. The connection is far from an invariable or even extremely frequent one.

Loomis[2] makes the statement that "postmortem studies teach that fatty degeneration of the heart is usually associated with obstructive changes in the aorta and the origin of the coronary arteries; while, as I have already stated, fibroid changes are usually associated with obstructive changes in the coronary arterioles." If this association is a frequent one, and if the degeneration of the ganglia depends upon obstruction of the small branches of the coronaries which go to feed the auricular walls, we certainly ought to find a very frequent connection of slow pulse with fibroid degeneration, which is not the case. Four such cases are in our table. Hilton Fagge,[3] among eleven autopsies made by himself where the walls of the heart were in a condition of fibroid degeneration, mentions two cases as having had a slow pulse, and among nineteen others found in the records of the Society finds two, which are those mentioned in my table. He says: "My cases, however, do not at all support the opinion that a slow pulse is to be regarded as a constant or even a frequent result of fibroid disease. These are problems which are still looking to minute anatomy and histology for their solution."

The intrinsic ganglia of the heart have been examined in but very few cases of this kind, and in only one microscopically (Jona, Case 32). That was not a typical one, inasmuch as mitral stenosis existed, which is likely to exhibit an apparently slow pulse when the heart is beating at a normal rate; and, indeed, it is stated that the heart beat nearly twice as fast as the pulse at the wrist; but since the minimum pulse (22), even if nearly doubled, would still have been slow, and as

[1] Berl. klin. Woch., 1885, p. 215.
[2] Transactions of the American Climatological Association, 1892, p. 73.
[3] Transactions of the Pathological Society of London, 1874, p. 64.

other observers find lesions of these ganglia in specially frequent association with valvular lesions, it might have been supposed that there would have been degenerative changes of the ganglia. But the reporter, who made a very careful examination, is not certain that the slight changes, chiefly in the chromatin of the cells, indicated anything more than such functional ones as have been found in other nerve cells from fatigue. Here again we are met with the opposing fact that in a large number of cases in which both sclerotic and degenerative changes in the ganglia were actually found, the pulse was rapid and usually weak.[1] Further histologic researches are required when cases presenting the appropriate clinical phenomena arise.

From a combination of the positive results of interference with the augmentor nerve fibers higher up in their course—*i. e.*, from fractures and dislocations and one or two cases of disease, and, on the other hand, the insufficiency of the common and obvious cardiac lesions to account for the phenomena—it may fairly be said that the *permanent or continued slow pulse is the result of a paresis of the augmentor nervous system*, depending either on a lesion anywhere in its course from the bulb down to and including the intrinsic heart ganglia, or on a localized weakness which in acute or temporary cases would probably leave no anatomic traces behind.

In the medical cases—*i. e.*, the strictly Stokes-Adams—it may be claimed with less confidence, but still with considerable probability, that the lesion is situated in the auricular ganglia and is of a degenerative character. It is likely to be dependent upon fatty degeneration of special small branches of the coronaries, destined for their nourishment. Why the special symptom should be at one time a rapid and at another, much less frequently, a slow pulse, is probably dependent on the extent and degree of advancement of the degeneration; but there is no more inconsistency involved than in the closely allied facts of degeneration of other nerve cells where we have absence of reflex excitability succeeding an increase—anesthesia to hyperesthesia or dementia to excitement. In fact, the transition from rapid to slow has been noticed in some of these very cases, and also in connection with the action of certain drugs. A very notable case is one reported by Platt,[2] where a young lady recovering from pneumonia had for a number of days a pulse which underwent very rapid tran-

[1] Ott, loc. cit. [2] Transactions of the American Climatological Association, 1892, p. 59.

sitions, by the dropping of successive beats, from a little above the normal (110) to considerably below (48). In a last and more severe attack, attended with much prostration and vomiting, the pulse, when it could be counted at all, went down to 40 or 50 for several hours until it changed to 92 and final recovery. In this case, and probably in many which resemble it in everything except the rapidity of the transitions, there is probably a good deal of pneumogastric influence at work.

Watson Williams,[1] in a paper on paroxysmal tachycardia, speaks of a case of pericarditis where the pulse fell from 108 to 52, then to 24, and sometimes even to 6. In another case the tracings showed the occurrence of prolonged asystole during attacks of tachycardia.

The slow pulse existing when there is evident general debility and nothing else, as in convalescence, dropping below the normal, together with the temperature, for a few days, as well as the low temperature often connected with the chronic cases, points to a condition of local cardionervous debility.

The augmentor system is in a condition of diminished resistance as regards the action of the pneumogastric, which is simply a regulator when the augmentors have their proper tone, but which, when their resistance is pathologically diminished, goes beyond the due balance of forces and produces the phenomena of the still slower pulse. Whether the original development of these conditions is due to a simple progressive increase of degenerative changes which have imperceptibly reached the effective degree, or to a rapid exhaustion of nerve centers by excessive stimulation analogous to the dilatation of the heart muscle under excessive exertion, cannot now be answered by anatomy. A sudden shock is capable, judging by symptoms, of producing impairment of function which requires days or weeks to recover from or which may be permanent; but it is not known at what point the slight temporary changes which have within the last few years been found in so many nerve cells, as a consequence of fatigue, pass into the degenerative ones that mark a chronic disability.

Without regard to the anatomic findings, there are some physiologic observations which show a very close analogy between the formation of the slow pulse in those cases in which the intermediate beats continue to be feebly represented, and the action of the vagus.

[1] Bristol Medical Journal, 1897, p. 122.

It was found by Chauveau,[1] and also by Vaquez and Bureau,[2] that certain small intermediate beats which could be seen in the cardiogram and, synchronously with this, in the jugular pulsations were referable to auricular contractions which were not communicated to the ventricle, and this condition of things was compared to what is found when the vagus of the horse is weakly stimulated—that is, the inhibition of the ventricular contractions, while the auricular are but little affected.

Pouzin[3] gives the same explanation of the weak beats, and Bristow[4] also suggests it without coming to a decision. Of course, this condition is fairly referable to the want of efficient reflex nervous connection between the auricle and ventricle, and it is not only possible but highly probable that this connection may be impaired not only by a permanent degeneration of the ganglia but by the temporary interference of the pneumogastric.

Moritz[5] describes a case where there was a jugular venous pulse of 76 to 78, with a radial of 30, and a number of weak tones in the heart. He entitles this "one-sided bradycardia," and thought it ought to have been due to a syphilitic neoplasm at the ventricular septum, but it seems much more like another instance of auricular pulsations persistent after the ventricle has taken up a slower rhythm—*i. e.*, that the heart was cut in two functionally in the transverse instead of the longitudinal direction.

It has been shown, as already stated, that the point of the heart, if fed, may be made to beat not only irregularly but rhythmically, but it is also found that when the ventricle has been "crushed off" by a tight thread the rhythm of the ventricle is no longer the same as that of the auricle.

Langendorff[6] even claims that such slight relations between the two segments of the frog's heart after the ligature, as are shown by a "regular succession of auricular beats"—*i. e.*, a number of auricular without effect on the ventricle, and then one auricular followed by one ventricular, which sends along a wave of blood through the aortas, are due to imperfect crushing that has spared some fibers.

Kronecker[7] also states that stimulation can be conducted (in the dog's

[1] Revue de Méd. and Lyon Méd., 1883.
[2] Mém. Soc. de Biol., 1893.
[3] Paris Thesis, 1898.
[4] Lancet, 1885.
[5] St. Petersb. med. Wochenschr., 1897, p. 301.
[6] Arch. f. Anat. und Phys., 1884, suppl.
[7] Verh. d. XV. Congress Inn. Med., p. 524.

heart) from auricles to ventricle by a single nervous bundle, and when this is ligatured the ventricles beat independently some three times slower until death.

These temporary and experimental resemblances of action, however, do not remove one of the main objections to applying the vagus theory to the *permanent* slow pulse, namely, that its inhibitory action is short, and soon overcome by normal augmentors.

The *paroxysmal manifestations of Stokes-Adams disease fit in much more easily with a theory of vagus irritation than does the permanent condition.* Such a theory, applied only to the paroxysms, calls for no lesions, gross or microscopic, of the bulb, since it is only a reflex center whence the inhibitory impulse takes its origin by transformation of any temporary sensory irritation within or without the nervous centers. Debove[1] reports the case of a patient whom he had observed for some years with a pulse of 36, who died in syncope; nothing is said of the presence of any paroxysm previously. The bulb was found perfectly healthy, the pneumogastric nuclei being specially examined by the microscope. The pneumogastric nuclei were examined microscopically in Prentiss' first case, although without the most delicate methods now in use, the result being negative.

A very interesting case given by Romberg,[2] from Heine, at too great length to be quoted in full, shows the probable action of the vagus in producing a temporary cessation of the heart's pulsation.

A man, aged thirty-six years, stated that his heart often stood still. At his next visit he was able to demonstrate the fact, for there was an intermission of five or six beats of the heart and of the pulse. The aspect of the patient showed that at the time something terrible was going on within him; he sat there as if thunderstruck, speechless, motionless, his eyes wide open, his consciousness unimpaired. He had a violent pain at these times on both sides of the thorax, extending to the neck and head. He knew of nothing except mental emotions, which had a tendency to produce the attacks, which were much more frequent on some days than on others.

The most accurate examination of the heart during the free intervals failed to demonstrate any abnormality in the rhythm, the sounds, and

[1] Soc. Méd. des Hôp. de Paris, 1888, p. 441. [2] Syd. Soc. Trans., vol. iii. p. 340.

the extent of the cardiac dulness. He lost strength, had vertigo, and died in a state of sopor.

The autopsy was made with great care by Rokitansky.

The nervous cardiacus magnus, which ascends from the plexus lying between the descending aorta and the pulmonary artery, was woven into a black knot of the size of a hazel-nut by the lax, pale-grayish cords forming the cardiac nervous plexus; before its entrance into the knot the nerve was thickened. The branches of the left vagus, which descend upon the anterior side of the left bronchus to the pulmonary plexus, proved to be dragged in the same way by an underlying nodulated dark-blue, lymphatic gland. The heart was of the usual size and tough. There were other enlarged and cretaceous lymphatic glands, one of which interrupted the phrenic nerve. The solar ganglion was very large. There were many pathologic changes in the brain and cervical spinal cord.

The pneumogastric is more effectual in reducing the activity of the heart's beat in proportion, "as the augmentor system is weaker. It is possible to greatly slow or even stop the heart in a weak animal by the use of a stimulus which in the vigorous is unable to do more than cause a comparatively slight and transient slowing, followed by a rapid and immediate escape. The heart of a dog or cat weakened by repeated inhibition very frequently toward the end of the experiment shows itself unable to escape effectively to a regular rate and force of beat."[1]

These physiologic observations show how the paroxysms in a case of slow pulse may be developed by causes which, acting against augmentors of normal resistance, would be inoperative.

If there were any increased reflex susceptibility on the part of the vagus, it would, of course, increase the intensity of the phenomena, but such an increase is not demanded by the hypothesis.

Some very suggestive experiments by Mayer and Pribram[2] illustrate the efficiency of what is, in such cases as we are able to assign any definite cause, one of the most common causes of the paroxysms—*i. e.*, digestive disturbances. By the aid of the usual registration methods they determined the action of gastric irritation in increasing the general vascular tension and in lowering the rate of the pulse. This

[1] Hough: Journal of Physiology, 1893, p. 161. [2] Stzber. der Wien. Akad., 1872, p. 104.

seemed to be due more to action upon the muscular and serous coats of the stomach than on the mucous, for irritation of the latter by chemical irritants or by cold had no effect upon the pulse, while with electric or mechanic irritants applied to the outside it was decided.

The most interesting observation as most closely simulating that condition which holds so prominent a place among our "gastric griefs and peristaltic woes"—*i. e.*, flatulence—depended upon the introduction of a rubber balloon into the stomach, and as the dilatation of this increased and diminished, so did the vascular tension, while the frequency of the pulse varied in the opposite direction.

It would be very desirable to apply the atropin test during the paroxysm for the purpose of deciding in each case how far the two factors of weakened augmentors and irritated pneumogastric might be involved, but so far as I have found this has not often been done. I regret extremely that I have not done it myself when the opportunity offered. One case, however, seems to be in accordance with the theory.

Kinkead[1] was called to see a man who was taken sick one evening with faintness and pain in the stomach, but without vomiting. The pulse was at first regular, but after another attack of faintness it became intermittent. The next day he vomited and had acute pain on pressure just below the ensiform cartilage, and the pulse had fallen to 6 per minute. The physician watched him for an hour, phonendoscope over the heart, finger on pulse, and watch in hand, while the pulse beat at this rate. Atropin was injected hypodermically and a mustard leaf placed over the stomach. After about an hour the faint feeling passed off, the pain at the pit of the stomach got better, and the next morning the pulse was 72. One cannot help regretting that he did not watch for another hour with the phonendoscope.

A day or two later there was a little tendency to irregularity, the joints became painful and swollen, but were relieved by salicylate of soda, after which there was no further trouble.

After looking over a considerable number of cases one finds that the origin or causes of this condition stated are so vague or so general in the great majority of them, that any attempt at statistics would have only an apparent precision. But it seems quite evident

[1] Dublin Journal of Medical Science, 1898, p. 4.

in looking at the list of cases with autopsy that essentially the same causes have been at work as in the degenerative diseases of the heart in general, except so far as valvular disease, the result of acute rheumatism, is concerned as an important factor, and even this is not entirely absent. The wear and tear of life in general are undoubtedly not without their effect, and alcohol also, but bradycardiacs are not to be found especially numerous among those who have suffered more than their neighbors, or, on the other hand, among those who have drowned their sorrow in the flowing bowl. Severe bodily efforts, not necessarily extremely prolonged, and mental and emotional strain, come the nearest to being frequent causes. The first of these is interesting in connection with the observations of Allbutt, Da Costa, Leyden, and others, where great strain with heavy weights and under conditions involving fixation of the thoracic muscle is a potent cause of dilatation and disease of the heart, but entirely without the clinical phenomena of the cases now under discussion. The latter, *i. e.*, psychic causes, have an interest as being frequently invoked in the origin of a condition almost the opposite, that is, Graves' disease with its extremely rapid pulse. It would seem that if certain shocks bringing to bear a strain upon the heart, and finding it in a condition of unstable equilibrium, were liable to disturb its rhythm in either direction.

Is the determining factor in such cases an augmentor paresis already present or closely impending?

A case reported by Strübing[1] is a very interesting one as showing quite clearly the origin of a well-marked instance of this kind at a much earlier age than usual.

A boy, aged fifteen years, well built and nourished, was fairly well and strong, except that he did not easily keep up with the other boys in running. On one occasion he ran a considerable distance, not to be late at school, was attacked by vertigo, and his face grew pale. He fainted and lost consciousness, but after awakening with a headache, walked home and went to bed, where he had another attack, with loss of consciousness and convulsions. This was the beginning of a series of attacks which involved no dyspnea or palpitation, but vertigo and headache. The heart was enlarged. The pulse usually 16 to 18, the contractions not of the same strength or same interval,

[1] Deutsch med. Woch., 1893.

dicrotic(?) (dicrotism is very rarely, if ever, seen in a well-marked case of this kind, and in the tracings given in this, although, to be sure, they were taken at a later period, there is not the slightest trace of it). There were several occasions of improvement and a falling back, psychic excitations being of distinct effect in bringing on severe symptoms, with a pulse of 14 or 12. With great care, especially as to effort, the pulse gradually rose to 44 at one time, but there were other relapses, and he finally died. At last a systolic murmur developed. In Prentiss' case there had been heavy lifting. Other cases are to be found in the tables.

In the etiology, as well as in other points, we find the weak heart with slow pulse coming very close to the weak heart with rapid and irregular pulse. Leyden,[1] after speaking of the symptoms of heart disease arising from overexertion, including irregular pulse and "pulse more frequent, or easily made so," mentions a rare group of cases of exhaustion connected with a slowing of the pulse to 40 or 30, and gives several cases. Sexual excesses are mentioned in a general way by some writers. My own experience would not point strongly in this direction, and I have found it mentioned distinctly but once in connection with the special case. There is no reason, of course, why it should not be placed among other depressing agents.

Saurel has written a thesis (Paris) on the permanent slow pulse in general and in particular in *surmenage et l'anemie*, but his cases relate more definitely to the latter factor.

PROGNOSIS. The moderately slow pulse of convalescence or in the course of acute diseases, especially in rheumatism, is particularly of little importance, not adding to the gravity of the cases, as judged by other symptoms. It is usually quite temporary under these circumstances. The same may be said of its occurrence with a slightly lowered temperature in mere debility.

The permanent slow pulse should lead to careful inquiry into the condition of the heart; and the presence of nervous symptoms, even so slight as transitory vertigo, would materially affect the prognosis. There are a good many of what may be called acute or subacute cases, which improve not only as regards the nervous symptoms, but also in the frequency of the pulse within a few days or weeks. They

[1] Zeitschr. f. klin. Med., 1886, p. 105.

are usually cases which originate in some special strain, and the recovery is complete.

Another group, and these are especially elderly or aged persons, get rid of the nervous symptoms, and, living a moderate life, experience no inconvenience from the slow pulse, which remains the same. They are not, however, to be looked upon as completely well, and are liable to a return of the paroxysms under bodily or mental stress or even without special known cause. The cases where very slight nervous symptoms still persist are to be classed with these.

In the fully developed disease, cases where the nervous symptoms remain, but perhaps leave the patient fairly comfortable in the interval, are eminently uncertain. No insurance company would look at them for a moment, and yet instances are by no means unknown where they live for years.

An instance, however, is reported by Flint,[1] in which a man whose pulse was supposed to have been slow for many years, and who had epileptiform convulsions, was not only looked at by an insurance company but accepted, nine and eight years before Dr. Flint saw him. A little doubt is thrown upon the genuineness of this case as an instance of Cheyne-Stokes by the fact that in the convulsions the pulse became rapid instead of slower.

Some writer has mentioned three and a half years as the probability of life, but a calculated average of that kind can have very little value, except as a matter of statistics. The study of the individual case, and in particular the severity of the symptoms and condition of the pulse during the paroxysms, would give much more important results. The great majority of such cases die during a paroxysm. The longest period I have seen mentioned was in a case of Osler's—thirty years.

Huchard[2] calls attention to three sets of cases. Those in which there is no *permanent* slow pulse, but which correspond to the type in the occurrence of the nervous attacks, the pulse at the time being slow. In these it may be supposed that the accelerators, while sufficient to carry on the beats at the ordinary rate under ordinary circumstances, are so near the point of yielding that the vagus easily overcomes them. Case 64.

[1] American Practitioner, vol. xiii. p. 1.

[2] Archives Gén., 1895, p. 257.

Those in which the nervous symptoms are but slightly marked, transient attacks of vertigo or weakness. Case 65.

What he calls "associated," which are simply the occurrence of Stokes-Adams with something else, without any special connection between them, or at least only such as is very common with other forms of heart disease, either the renal setting up the cardiac, as happens in some cases, interstitial nephritis or the vascular degeneration lying at the foundation of both; or, on the other side, the kidney suffering from congestion. Such a case is reported by Whitridge.[1] An important therapeutic observation gives rise, as has happened often enough before, to rather a loose piece of pathologic classification. Several cases are called "uremic," in which this diagnosis rests solely on the scanty urine and the great improvement which takes place on a milk diet and consequently increased excretion.

The treatment of the permanent slow pulse consists in rest, which is to be more or less complete according to the special case, from the most absolute upward. Diet, tonics, and such regulated exercises as have been found beneficial in other forms of heart disease are also of use here. Cardiac tonics have been found of some value, although there is no specific. The nitrites have been favorably mentioned in some cases. Digitalis, the beneficial action of which in most cases of heart disease consists in its slowing the pulse, has in a few cases resulted in quickening that which is already too slow, an action which it is not difficult to understand when we recollect that the tonic action of this drug consists not only in increasing the activity of the pneumogastric and the vasomotors but to a certain extent that of the augmentors also. In these cases it may happen that the balance is so adjusted that the latter effect outweighs the former.

Belladonna has proved a distinct failure for the treatment of the permanent slow pulse.

The prophylaxis of the paroxysm consists in carefully adjusting the load to the weakened muscular system that has to carry it, and in avoiding the causes of exciting the reflex activity of the vagus, in particular muscular strain and digestive disturbance. Potassium bromide has been suggested on theoretic grounds to diminish reflex activity.

[1] Boston Medical and Surgical Journal, 1900, p. 329.

In the developed paroxysm cardiac stimulants like ammonia and the nitrates are to be used, and especially atropin, which should be given subcutaneously in the dose of one or two milligrams. The recumbent posture, of course, favors the return of blood to the brain. One patient found that he could ward off the fits by getting on his hands and knees and allowing his head to hang down.

Comby[1] reports several cases of slow pulse in old persons where the syncopal, epileptiform, and vertiginous attacks disappeared on rest and good feeding without change of pulse.

[1] La Semaine Médicale, 1892, p. 265.

TABLE I.—CASES OF PERMANENT SLOW PULSE WITH NERVOUS, SYNCOPAL, OR DYSPNEIC PAROXYSMS, IN WHICH AUTOPSIES WERE MADE.

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
1	Prentiss. Trans. Assoc. of Amer, Phys., 1889.	M. 54	36—12	Sounds normal, sphygmograms.	Faint, short loss of consciousness, cyanosis.	Temp. slightly diminished.	Tobacco; malaria; early paroxysms 1887.	Improved; relapsed; cont'd paroxysms; delirium, death 1890.	No fatty degen.; no atheroma coronaries.	Nothing remarkable.	Ganglions no change; slight swelling of cardiac branches of vagus.
2	Duncan. Med. Commentaries.	M. 54	26—9	.....	Exhaustion; fainting; convulsive attacks.	.....	.....	.....	.....	Watery fluid in ventricles; gelat. appearance some parts of pia.	
3	Gibson. London Med. Gaz., 1838-39. vol. 1	M. 70	22—16	Very feeble in paroxysms	Pallor; cyanosis; loss of consciousness.	.....	Slight fit 20 years before.	Last 8 years fits more frequent, died in one.	Slight ather'ma coron.; heart large; aorta dilated and atheromatous lower part	Congested.	
4	Holberton, Med.-Chir. Trans., vol. xxiv.	M. 64	33—7 60 before accident.	.....	Fainting fits; dyspnea.	.....	Fall from house; injury to neck.	Died in syncope 5 years later.	Large & weak; lining of vessels thickened.	Congestion of medulla oblongata from enlargement of odont. process.	R. middle cervical ganglion unusually large.
5	Cain. Charleston Med. Soc., 1849.	M. 45	34—38	Sounds normal.	Pseudo-apoplectic.	.....	3 years before, after exposure (?) with fluttering.	Later dyspnea, palpitation, exhaustian, increased frequency of fits.	Much fluid in pericardium; enlargement softening; aorta cong'ed.	Healthy; slight hyperemia.	
6	Jacobi. Trans. Assoc. Amer. Phys., 1889.	M. 54	28—18	Much changed; 4 or 5 sounds.	Syncope.	Temp. diminished.	.....	.....	Atheroma of art.; fatty degen. of heart; heart ganglia enlarged, hard and calcareous.		
7	Edes. See text. Case 1.	F. 50	56—14	Irreg. weak, area not enlarged.	Syncope; loss of consciousness at times.	Anemic; temp. about normal.	Shocks, grief, fainting.	Paroxysms continued; died in one.	No fatty degen.; very little atheroma; coronaries normal.	Normal.	

8	Stackler. Rev. de Méd., 1882, p. 204.	F. 53	40—28	Two cardiac revolutions to each cardiac beat; irreg. souffle.	Heart stopped; then 80; pain; sometimes loss of consciousness; cyanosis.	Vomiting	Previous to 1880 nervous attacks with sometimes loss of cons., prob. hysteric.	For 5 or 6 years palpitation, pain in precordia.	Milky patches on pericardium	Tumor of mediastinum involving r. vagus; vagus hard, red, swollen.	By microscope no alteration of vagus fibers.
9	Lepine. Lyon Méd., 1889, vol. xliii p. 315.	M. 65	34	1st complete beat fol. by 1 or 2 pair; sometimes a 5th; impulse with first sound.	Loss of consciousness, like calm sleep; not followed by any inconvenience.	.....	15 attacks in 18 months.	Later depression for half a day after attacks; died suddenly; slight convulsion of face.	.....	Narrowing of vertebral canal prominence of apophysis suf. to cause some comp. of v. side of protuber'nce and bulb.	
10	Tripier. Lyon Méd., 1883, vol. xliii.	...	60 60—12	.....	Epilepsy.	.....	.....	.....	Completely negative.		
11	Gibbings. Lancet, Feb. 14, 1883.	M. 66	Intermittent ever since he can remember. 44—12	No evidence of disease.	First indication of recurrence failure of usual beat, then epileptiform, face pale, patient had an aura.	Temp. a little below nor.; resp. 18—20	Anxiety, worry.	Improvement, relapse; fainted at school; death.	Arteries remarkably free from atheroma; valves and muscular walls healthy; coron. pervious.	Other organs normal.	Autopsy by Moxon. Atropin did no good.
12	Claybaugh. New York Med. Journ., 1895.	F. 55	40	Palpitation.	Epileptoid.	.....	Bronchitis (grippe).	Better than usual 2 or 3 days; died suddenly.	No valv. dis., one coronary had small cal. deposits throughout its course (see last column).	.....	Roof of arch of aorta chronically inflamed; small calcareous patches in aorta; pulmon. vein acutely inflamed.
13	Sendler. Centralbl. f. klin. Med., 1892, p. 642.	F. 35	40—37—24—22	Systolic murmur.	Fainting fits.	.....	Gener'l debility and fainting fits, 6 months.	Increased pulse to 30; died in fit.	Heart large, embedded in fat; myocard. flabby; valves normal; narrowing of pulm. artery by fibroma.	Wet brain congested.	
14	Hanot & Luzet. Soc. Méd. des Hôp. de Paris, 1899.	M. 72	Diagnosis of slow pulse, 36	Some "faux pas."	Vertigo, sometimes unconscious; a few times convulsions.	.....	Not good habits; sudden attack of unconsciousness with convulsions.	Frequent vertigo, two syncopes; sometimes loss of consciousness; no convulsions; sudden death.	General atheroma.	Induration of small vessels in cerebellum.	

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
15	Siredy. Soc. Méd. des Hôp. de Paris, 1899.	M. 58	40—32—28	.....	Epileptiform.	Alcoholic	.....	.....	General arteriosclerosis.	Carotids and arteries at base hard; no lesion of cerebrum, cerebellum, or cord; bulb manifestly congested.	
16	Adams. Dublin Hosp. Rep., vol. iv., 1827.	M. 68	Usually 30: slower than usual in attacks.	Oppression in breathing.	Apoplectiform; complete insensibility; no paralysis.	.....	....	At least 20 attacks in 7 years; died in one.	R. aur. much dilated; aortic valves thick'd; r. vents. fatty; ven. very thin, cov. with fat; fatty degen.		
17	Risdon. Lancet, Mar. 27, 1897.	M. 38	70 24-30	Normal.	Faintness; brief loss of consciousness; slight tonic spasms.	.....	Athletic; sudden faintness when walking.	Improvement, collapse; intermittent pulse; died three days later.	Coronaries norm.; l. ventr. sl. hypert.; streaked with fat at one point near apex; small patch atheroma in one part aorta.		
18	Parkes & Cadge. Quain, Med.-Chir. Trans., vol. xxxiii.	M. 54	30 irregular.	Slight enlargement, first sound short; both muffled.	Faintings; extreme dyspnea.	Temperate.	Not fat; winter cough, last two winters worse; dyspnea.	Died suddenly; syncope.	Larger than natural; fat on surface walls of vents. soft and friable; aorta atheromatous; r. coronary esp.		
19	Bence Jones. Trans. Path. Soc., vol. vii	M. 33	Feeble 36—28	Sounds distant, impulse feeble.	Fainting fits; some spasmodic action; not perfectly insensible.	Anemic.	Fainting fits frequent for 6 weeks.	....	Fibrous deposits in mus. sub.; l. cavity dil., wall atrophied; columnæ carneæ atrophied.		
20	Ogle, Trans. Path. Soc., vol. viii.	M. 30	48 regular.	Action feeble, sounds distant, muffled,	Epileptic attacks.	Emaciated; anemic.	Had had rheumatic fever following diarrhea, epileptic attacks.	.....	Fibrous deposits in muscular substance; valves and orifices normal; sl. amt. athero. at root of aorta.		

21	Regnard. Case 12. Thèse de Paris, 1899–1900.	M. 55	26	Sounds normal.	Vertigo, loss of consciousness, convulsions.	.....	For 4 years vertigo; loss of consciousness followed by general convulsions.	Died in pseudo-epileptic attack with pulse 94 and stertorous respiration.	Fatty overgrowths and degeneration; coronaries narrowed and atheromatous.	Edema of brain.
22	Regnard. Case 16.	M. 30	28	Hypertrophy: impulse violent, no souffle.	Dyspneic, anginous, syncopal.	Drinker.	Infantile paralysis; dyspepsia; rheumatism; syncopal attacks.	Died in syncopal attack.	Large, fatty; openings of coronaries normal; left ventricle thick; acute aortitis.	Brain (carefully examined) normal.
23	Regnard. Case 19.	M. 60	20	Pulse small, average tension and force.	Loss of consciousness.	.....	For 6 years attacks of loss of consciousness without convulsions.	Death by arrest of respiration; edema of glottis	Hypert. and dil. with chronic deforming end-arteritis; coronaries dilated but healthy.	Thickening and dilatation of vessels at base of brain.
24	Williams and Quain. Med.-Chir. Trans., vol. xxxiii., p. 167.	M. 48	32—24	Extended dulness, feeble impulse, 1st sound not loud, 2d distinct.	Syncope.	Thin and feeble.	.....	Lived 2 years after first observation; fits continued; died in one.	Heart 17 oz., yellow, fat externally; soft, pinkish-yellow, mottled; atheroma mitral, aorta, coronary.	
25	Bright. Med. Reports, p. 270.	M. 45	30—32	.....	Epileptiform.	.....	40 days before entering hospital edema of legs.	Repeated attacks; delirium; died of edema of lungs.	Heart large, thin; valves healthy; one small patch of disease near arch of aorta.	No clot or other organic lesion; black (carbonaceous) deposit in arachnoid; no remarkable ossification of arteries.
26	D'Arman. Riv. Ven di Sc. Med., 1887.	M. 58	20	Normal, except weak and not clear.	Epileptiform.	Dil. of pupil; alcoholic	Obscure vision; loss of consciousness; slow pulse; nurse thought pulse stopped during attacks.	Cough; digestive troubles; desire to vomit; later epileptiform.	R. vent. and aur. dilated; l. vent. nor.; walls much thickened; consistence perhaps harder than normal; diffuse fatty degeneration; coronaries at aorta normal except a little displaced at orifice.	Carotids slightly atheromatous; other art. not so; asymmetry of medulla; sup. left cervical gang. a little larger than normal.

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
27	D'Arman. Riv. Ven. di Sc. Med., 1887.	F. 76	44 in febrile attacks; 44—24	No examination noted; radial pulse synchronous with impulse.	Epileptiform.	Fat, anemic; temp. 36—38	While walking sudden faint with cyanosis.	Several after-attacks within 24 hours; died suddenly after vomiting breakfast.	L. vent. dil.; coronaries with some sl. atheromatous spots; l. auric.-vent. orifice enlarged and hard; aorta sl. dil.	Edema of brain; vagi and sympathetic normal except edema.	
28	D'Arman. Riv. Ven. di Sc. Med., 1887.	M. 74	32	Systolic murmur at apex; impulse weak.	Faintings.	Pellagrous.	Prostration; constriction of chest, nearly fell; syncopal attacks repeated.	Improvement; left hospital; pulse continu'd slow; died in syncopal attack	Slight atheroma of aorta and valves; mitral insufficient by atheroma.	Serum and adhesions in pleura; l. post. lobe, cerebell. and r. anterior lobe softened.	
29	Petrucci. Gaz. d. Ospedale, 1898.	M. 52	24—14—12	Somewhat irregular; sounds weakened, but no murmur.	Syncope, generally after fatigue.	.....	For 3 or 4 mos. frequent, transient inclinations to faint; sleeplessness; short breath.	Died in apoplectic attack.	Atheroma aorta; carotids, coronaries, valves suffic'nt; some patches atheroma; myocardium pale, some spots callous, myocarditis	Bulb not examined.	
30	Aron. Berl. klin. Woch., 1891, p. 620.	M. 62	Tracing given, 24	Dulness increased; slight systolic murmur; slight murmur in interval.	Inclinations to faint.	Stout, pale.	....	Epileptic attacks three or four times a week; sudden death.	Large, fatty on surface; brown pigment; mitral stenosis; coronaries narrowed; calcified aorta.	Cerebral hemorrhages; hemorrhages in retina	No history to show dropping out of beats; by movements of sphygmogram, pulse not absolutely regular.
31	Boffard. Arch. de Méd. Expér., 1890, p. 90.	F. 27	28—30; rose to 40–50 in febrile condition	First sound prolonged; never "coupled rhythm" or arhythmia.	Epileptic.	.....	Dyspepsia; slight dyspnea; well-marked epileptiform attacks.	Died in an attack only 11 days from first epileptiform attack.	Some dil. right cavities.	Walls of cranium and mem. thickened; occip. foramen dim. in ant.-post. diam. down to 3d cer.; scarcely adm'd little finger; dil. rt. cavities of brain.	

32	Jona. Riv. Ven. di Sc. Med., 1898.	M. 46	26—30—22	Friction sound; sounds distant, dull, more frequent than radial; almost exactly double.	Epileptiform; cyanosis; extreme slowness of pulse.	Extreme dil. of pupils.	Pulse in health 75; became afflicted with dyspnea, oppression, prostration.	Died in unusually severe attack.	Rough patches on pericardium; l. vent. sl. distended; walls hypertrophied; sl. thickening of aortic valves; mitral stenosis; coronaries normal; no atheroma anywhere; some sclerosis cardiac muscle.	Slight edema of brain.	
33	Cornil. Gaz. des Hôp., 1875, p. 509.	M. 75	28—30	Heart same as pulse.	Dyspnea, some convulsive movements; consciousness sometimes lost.	Weak, pale.	Lost appetite; vomited; emphysema and bronchial catarrh.	.....	Size normal; no lesion orifices; complete fatty degeneration; aorta & valves sl. atheromatous.	Brain pale; adhesions of dura mater.	Fatty degeneration of pancreas
34	Worthington. Lancet, 1840–41, ii. p. 336.	M. 45?	75—40 or less.	.....	Dyspnea, prostration.	.....	.....	Died in unusually severe attack.	Fatty, valves normal.		
34a	Pope. Veterinarian, 1835.	Horse	10	Strong, bounding rattle which made whole chest shake.	Heart ceased beating and horse fell down.	.....	.....	Killed.	.....	Dropsy of spine in cervical region.	

TABLE II.—CASES OF SLOW PULSE, WITHOUT WELL-MARKED PAROXYSMS, IN WHICH AUTOPSIES WERE MADE.

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
35	Goddard Rogers Canstatts Jahrb., 1857, p. 199.	...	48—28	.....	.....	.....	.....	.....	Cicatrices in septum.	.....	
36	Yeo. Lancet, 1802, p. 913.	M. 45	36	Apex in natural position; loud systolic murmur, then two short sounds.	.....	.....	.....	.....	Pericardium uniformly adherent; mitral stenosis; aortic valves thickened; heart flabby; right ventricle thin.		
37	Spencer. Prentiss, Case xxxvii., Boston Med. and Surg. Jour., 1834.	M. 50	Much slower than normal.	.....	.....	.....	Accident, fell on neck and head.	Complete sensory and motor paralysis below head; died in 48 hours.	.....	Dislocation between 2d and 3d cervical vertebræ.	
38	Abercrombie. Disease of Brain and Cord, Case cxviii	M. Soldier.	Slow, languid.	.....	.....	.....	Pain in back of head; giddiness; violent headache.	.....	.....	Vessels of cerebellum turgid; coagulum under cereb'm.	
39	Abercrombie. Prentiss, Case xxiv.	F. 6	30—40	.....	.....	.....	.....	Headache and right side convulsed.	.....	Hydrocephalus and tubercles in l. cerebrum.	
40	Bright's Med. Reports, p. 355. Prentiss, p. 135, Case xxv.	M. 49	36—42 later 44—78	.....	.....	.....	Had had blows on head; headache.	Giddy, wandering, drowsy.	Heart small; valves normal.	Brain adherent at right temple and indurated in spots.	
41	Abercrombie, p 89. Prentiss, Case xxviii.	16 mos.	Remarkably slow.	.....	.....	.....	Injury to back of neck.	Paralysis, convulsions; died in fit.	.....	Fluid in the ventricles; abscess at summit of medulla, where it was crossed by the pons.	
42	Prentiss, Case xxix.	M. 47	48	.....	.....	Respiration 13.	.....	.....	.....	Fract. between 4th and 5th cervical.	
43	Prentiss, Case xxx.	M. 20	40—50	.....	.....	.....	Fall; complete palsy.	Lived 3 days.	.....	Fracture 5th cervical; compression of cord with sanguinolent striæ.	

44	Schuh. Med. Gaz., vol. xxxiii. Prentiss, Case xxxiii.	M. 33	30	.....	.....	.....	Fall; neck deformed, painful; died on 12th day.	.....	.....	Luxation between 4th and 6th cervical.	
45	Schuh. Med. Gaz., vol. xxviii. Prentiss, Case xxxiv.	M. 35	Feeble and slow.	.....	.....	Respiration feeble and slow	Fall; palsied.	.....	.....	Luxation between 5th and 6th cervical; softening of medulla.	
46	Abercrombie, p. 264. Prentiss, Case xxxv.	M. 35	30—40 Shortly before death.	.....	.....	.....	Gradually palsied two years; sight and hearing affected.	Atrophy of two right limbs; short time before death pulse and respiration became slow, lost speech and power of swallowing.	.....	Brain and viscera most healthy; cervical cord hard and like cartilage; membranes red.	This seems to have been subacute anterior poliomyelitis with bulbar paralysis.
47	Nieden. Trans. Clin. Soc., London, vol. vi. p. 75.	M. 60	Gradually fell to 40.	.....	Temp. fell to 81.	.....	Fall down staircase; complete paralysis lower extremities, chest, and greater part of trunk. Anemic.	Progressive lowering of pulse and temperature; death on 11th day.	Distended with fluid blood.	Dislocation without fracture of 1st dorsal; compress'n of corresponding portion of spinal cord.	
48	Stokes, Case ii. Dublin Quart., 1846, p. 73.	M. 50	Very slow.	Valvular murmur.	.....	.....		Death apparently from syncope.	Aortic valves thicken'd; ventricle soft and flabby; covered by very thick layer of fat.		
49	Debove. Soc. Med. Hôp. de Paris, 1888, p. 441.	...	32	.....	Nothing said of an epileptiform attack.	.....	.....	.....	.....	Bulb perfectly healthy; examination of pneumogastric nuclei, nothing abnormal.	
50	Hutchinson. London Hosp. Rep., 1866.	...	50	.....	.....	.....	.....	.....	Fracture of cervical spine.		
51	Tyrrell, London Med. and Phys. Jour.	M. 24	40—55—50—35—20	.....	.....	.....	.....	.....	Fracture 4th cervical; small clot on dura; extravasation in cord.	Blood on surface of cerebellum; superficial cardiac nerves involved in coagulated blood.	

TABLE III. CASES OF PERMANENT SLOW PULSE, WITH NERVOUS, SYNCOPAL, OR DYSPNEIC PAROXYSMS, BUT WITHOUT AUTOPSIES.

No.	Reported by	Sex and age	Pulse.	Heart	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
70	Cooper British Med Journ., 1870, vol. [illegible] p. [illegible]	M 67	37 26 28	.....	Faintness and indigestion.	.....	.....	Died suddenly.			
71	Bull Acad Roy de Méd	F 45	18 36	Normal.	Epileptiform.	.....	.....	Died in epileptiform attack.			
72	British Med Journ., 1870, vol. 1 p. 113	M 52	22	.....	Prolonged fainting fits.	.....	.....	Fell dead after some slight excitement.			
73	W. Henry Day British Med Journ., 1870, vol. 1 p. 114	M 79	22	For 4 minutes beat 4 times a minute.	Tendency to syncope; convulsive fits	.....	Pulse has been for 9 mos. 22, full, fairly strong and regular.	Fits increased in frequency; died exhausted			
74	Boyce British Med Journ., 1884, p. 156	M 28	24 14	.....	Convulsions.	.....	Violent pain in head; syphilis; fell in convulsions, tonic and clonic spasms.	Vomiting and convulsions continue; on one occasion pulse totally absent 15 seconds; death.			
75	Trousset de Fontaine Schmidt's Jahr., 187 188.	...	12 14	.....	Epileptiform.	.....	.....	Died suddenly.			
76	Strubing. Deutsch med. Woch., 1898.	M. 16	16 18 12	At last a systolic murmur developed.	Vertigo; fainting.	.....	Given in more detail in text	Died.			
77	Strubing.	M. 70	50 40	Weakness of heart, dil. slight mitral systolic murmur.	.....	.....	Rheumatism several times.	Death in sopor.			
78	Strubing	M. 48	40 32 28 24	.....	Vertigo; general depression temp below normal; loss of consciousness	.....	Improvement after walk of several hours; pulse 28 24	Lived for some time comfortably if avoided exertion; died in about a year.			

61	Tripier. Revue de Méd., 1884 and 1885.	F. 68	24—10	Occasional "faux pas;" small second beat 1.2—1.2.	Epileptiform and syncopal attacks.	.....	Cachectic, probably organic disease of stomach.	Death.	
62	Regnard. Thèse de Paris, 1889–1890. Case xxi.	F. 65	25—28	Diag., fatty degeneration.	Epileptic convulsions, pulse 5–6.	.....	With tonics, pulse up to 35; two years carried on occupation.	Died in fields in pseudo-epileptic attack.	
63	Rotureau. Union Méd., 1870, p. 331.	M. 72	48 28—18—16	No other heart signs.	Syncopes.	.....	Much disturbed by losing office.	Died.	
64	Huchard. Arch. Gén., 1895, p. 257, abs. 1.	M. 54	80—30	First sound long and vibratory followed by two incomplete systoles; intermitting and irregular.	Vertigo and prolonged syncopes with convulsive movements and slow pulse.	.....	After 6 or 8 wks. in one day pulse went down to 24, varied up to 60 or 65.	Death.	Arteries hard.
65	Huchard, Potain. Arch. Gén., 1895, p. 257.	M. M'dle aged	Very low	.....	Slight weakness to which attached no importance.	.....	Appeared well.	Died suddenly in office.	Probable disease of valves, arteries, and myocardium.
66	Huchard, Potain. Arch. Gén., 1895, p. 257.	M. 67	45	.....	Fatigue and fainting on trying to make toilet.	.....	Face got pale and pulse completely disappeared.	Died suddenly.	
67	Strübing. Deutsch med. Woch., 1893.	M. 53	Slow	Hypertrophy and dil. both ventricles.	None.	.....	.....	.....	
68	Peacock. Med. Times and Gaz., 1864, p. 31.	M. 53	28—30	Dyspnea on exertion; prolonged rest between beats.	Syncope.	.....	Cramps in legs; travelled upward; had had rheumatic fever; moderate drinker; not smoked recently.	Lived several years; for four years no fit; pulse rose on exertion or excitement; sudden death; valv. disease?	
69	Peacock. Med. Times and Gaz., 1864, p. 31.	M. 70	25—30	Nothing unusual.	Apoplectiform; syncope.	.....	....	Syncope; sudden death.	
70	Peacock. Med. Times and Gaz., Jan. 9, 1864, p. 31.	...	for years.	Correspond. to radial; reg., strong.	Occasional syncope; epileptiform.	.....	Had led an active life; bodily exertion or excitement increased frequency of pulse	Died in sudden syncope 7 years after slowness first noticed.	
71	Edes. See text, Case II.	M. 80	70—26	Interpolated beats.	Attacks of unconsciousness.	Ch.-St. resp.	Fair general health.	Died with "cold," cough, slow and irreg. pulse.	

TABLE IV.—CASES OF SLOW PULSE NOT RESULTING FATALLY.

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
72	Stokes. Dublin Quarterly, 1846, p. 73.	M. 68	28—30	Dilatation; some irregularities of pulse and imperfect contractions: jugular pulse	Repeated pseudo-ep. attacks not followed by paralysis.						
73	Sorbets. Gaz. des Hôp., 1883, p. 699.	M. 62	28—32	Slight souffle at base.	.....	.....	Fatigue; vigorous; syncope after great fatigue; later vertigo, near falling.	Gradual improvement; pulse rose to 68–70; went back to work and continued well.			
74	Schuster. Deutsch med. Woch., 1896, No. 30	14	Slow.	Systolic murmur.	.....	.....	Acute rheumatism; attacks of slow pulse; fall of temperature; respiration slow, Ch.St	Complete recovery.			
75	Walker. Peoria Med. Monthly, 1881–82, p. 255.	M.	9½—14	.....	.....	.....	Collapse; sunstroke; malaria; paroxysms about every 12 hours; pulse declined with rise of fever, and vice versa.	Recovery.			
76	Foote. Med. Reporter, New York, 1809.	M. 24	14—30	.....	.....	.....	Mowing and drinking water freely; oppression of breathing, sighing resp., delir.; loss of vision, of consciousness.	Pulse slow, ten days; recovery.			
77	Somerville. Practitioner, London, xxi. p. 186.	...	25	.....	.....	.....	Indigestion (?) salt fish; good, not robust, health; temperate, not smoker, business worry.	Improved; remained in perfectly good health.			

78	Flint. Amer. Pract., 1876, vol. xiii. p. 1.	M. 52	26	.....	Temperature slightly diminished.	.....	Felt badly after active exercise and cold ride.	Pulse rose to 80, normal.	Judging from the effects of cathartics, due to intestinal trouble.
79	Flint. Amer. Pract., 1876, vol. xiii. p. 1.	M. 46	48—38	.....	.....	.....	In health 70–75; sick headache and malaria; when he felt quite well not more than 50.	Gradually became more frequent up to 74.	
80	Tillaux. Gaz des Hôp., 1876.	...	21	Decided cardiac sympts.	Syncope.	.....	Pulse in health not known.	Wanted to leave hospital.	
81	Oliva. Riv. Ven de Sc. Med., 1895, p. 79.	W. 82	34	Hardness of arteries.	Stenocardiac; epileptiform.	.....	From 30 to 50 (age) severe headache; after 50 good health; pale; sudden attacks with suffocation and oppression.	Calm appearance; sensorium normal.	
82	Kinnicutt. Proc. Assoc. Amer. Phys., vol. iv.	M. Middle age.	40—30—13 7	Pulse in radials corresponded with heart; mitral insufficiency.	Epileptiform seizures with slower pulse.	.....	In active business; fairly good health.		
83	Osler. Lancet, Feb. 27, 1897, p 623.	...	30	.....	Vertigo and loss of consciousness.	.....	Got better; still has bradycardia, but vertigo not so troublesome.	Later has had as many as 25 attacks of vertigo, and pulse still 30.	
84	St. Geo. Mivart. Lancet, Jan. 3, 1885.	...	20	Reg., tolerably full and firm; impulse almost.	Epileptoid.	.....	.....	Heart supposed to be fatty.	
85	Huchard. Arch. Gén., 1895, p. 257, obs. 1. Gaucher.	M. 65	16—20 later 60—64	.....	Vertigo; loss of consciousness; if he stands too long bilat. convulsions.	.....	Great eater and smoker; chronic aortitis.		
86	Huchard. Arch. Gén., 1895, p. 257.	F. 67	14	No clear signs of arteriosclerosis.	Loss of consciousness.				
87	Huchard. Arch. Gén., 1895, p. 257.	M. 62	80—44	General arteriosclerosis; aortic narrowing.	Syncopal and epileptic attacks.	.....	.....	Atheroma of aorta and other arteries.	

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks.	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
88	Huchard, Potain. Arch. Gén., 1895, p. 257.	... 50	20	Irregular.	Slight attacks insomnia, a little precordial distress; pulse 12-16 lasting several days.	.....	Pulse slow six years.				
89	Huchard, Potain. Arch. Gén., 1895, p. 257.	M. 52	45—50	.....	Slight attacks with slight slowing of pulse (40); extreme paleness of face.						
90	Noble. British Med. Journ., 1879, vol. ii. p. 874.	M. 96	36	.....	Syncope if long upright.						
91	Edes. See text, Case III.	M. 50	36—25	Interpolated beats at first.	Epileptiform.	.....	In hospital when seen only once.				
92	Handfield Jones Lancet, 1876.	M. 62	36—23	.....	Temperature subnormal; unconscious spells.						
93	Handfield Jones Lancet, 1876.	...	36—23	Every few seconds a distinct beat followed by a weak one.	Epilepsy; perhaps also syncope.						
94	Peacock. Med. Times and Gaz., Jan. 9, 1864, p. 31.	...	28—30	Aortic valve.	Occasional syncope or epileptiform.						
95	Debove. Soc. Méd. Hôp. de Paris.	M. 81	32	.....	Syncope.	.....	Usually good health; long walk; syncope.	Dyspnea like that of uremia; great improvement under milk diet; urine scanty; no albumin.			
96	Sonrier. Gaz des Hôp., 1884, p. 138.	M. 55	32 irregular.	Palpitation at various times.	Vertigo; a little dyspnea.	.....	Retired capt., great smoker; had had profound anemia in 1881; noted pulse 55 or 60.	Considered himself well except great slowness of pulse.			

97	Baranowitz. New York Med Record, 1881, p. 670.	M.	40	.....	.....	.....	Small thin man; op. strang. hernia; pulse 64 and 103.	Later pulse: lying, 42 sitting, 48 standing, 45
98	Comby. La Sem. Méd., 1892, p. 265.	F. 79	Slow.	.....	Vertigo.	.....	Urine, no sugar; slight trace albumin; urea less than 5 per diem; phosphates diminished.	Great improvement on milk diet: urea and phos. rose to normal.
99	Jackson. Bost. Med. and Surg. Journ., 1869, p. 376.	M. 53	60—20—16 Once counted 6 in half minute.	Sounds muffled and distant; perhaps slight systolic souffle.	Pale, weakness and giddiness, so that he would fall unconscious a minute or so.	.....	Healthy looking farmer.	Felt better and pulse quicker; hands and feet cold, particularly when pulse slow.
100	Greenhow. Med. Times and Gaz., April 30, 1864.	M. 32	48	Palpitation incor.; cardiac dul.; loud diastolic murmur.	.....	.....	.....	Decided improvement in health; pulse never varied from 48
101	Brown. British Med. Journ., 1879, vol. ii. p. 1020.	M. 70	124—17	Aortitis?	....	.....	Syncope if assumed erect posture.	First seen in febrile attack; pulse 110, temp. 102; for months pulse did not exceed 17.
102	Bantock. British Med. Journ., 1879, vol. ii. p. 1020.	F. 65	46—36	Healthy and regular.				
103	Squire. Med. Record, Nov. 26, 1888.	M. 80	28 24—32	Hypertrophy; arteries hard; no intermediate beat.	.....	.....	Ten years ago heart trouble.	Excell't health with uncommon vigor for his age; short breathed if he makes much exertion.
104	Prentiss. Quoted without reference.	M. 70	24—3	.....	Attack of spasms.	.....	Had had rheumatism; pulsations diminished in frequency for a time 3 in a minute.	Much prostrat'd but seemed improving.
105	Mayo. London Med. Gaz., 1838, 1839; vol. i. pp. 123–155.	M. 52	3 —30 –27	Ventricular disease; giddiness,	Ep. with transient giddiness; continuation of process short.	.....	Syncope.	Condition same.

No.	Reported by	Sex and age.	Pulse.	Heart.	Paroxysms.	Remarks	Origin or early symptoms.	History.	Postmortem appearance in heart and vessels.	Postmortem appearance in brain and nervous system.	Remarks.
106	Peaslee, New York Med. Jour., vol. xxiii.	Physician.	38	.....	Pain in occipital region	.....	.....	When ceased the use of tobacco pulse rose to ordinary rate.			
107	Peaslee, New York Med. Jour., vol. xxiii.	M. 45	40	.....	Pain in occipital region.	.....	.....	When ceased the use of tobacco pulse rose to ordinary rate.			
108	Flint. Amer. Pract., vol. xiii.	M. 35	40	Negative.	Faintness; no fit.	.....	Violent fit of coughing from food in larynx; vomiting; great prostration.	Violent strain: in two or three weeks usual health; heart healthy; died some years later of typhoid.			
109	Strübing. Deutsch med. Woch., 1893, pp. 4 and 5.	M. 24	64—68	Irregular and dicrotic, some dil.	Temperature very slow, below normal.	.....	Soldier, blacksmith; hard work 4 days before.	Gradual increase in frequency; recovery.			
110	Schuster. Deutsch med. Woch., 1896, p. 484.	4	.....	Small and arhythmic.	Temperature diminished.	.....	....	Another series of attacks in the morning; pulse not so much diminished; recovery.			
111	Edes. See text, Case IV.	M. 50	36—25	Interpolated beats.	.....	.....	Close application to business; several attacks of fainting with slight convulsions; frequent vertigo.	Walks and does light work; no vertigo; no fainting a year.			
112	Prentiss. Trans. Amer. Physicians. vol. iv.	M. 83	36	Systole; irregular, double or treble sound	.....	.....	Faintness and vertigo; may fall with momentary unconsciousness.	Now not more than one attack a year; recently married.			

113	Worthington. London Lancet.	M. 70	28	Feeble and irregular.	Dyspnea three years.	.....	Normal pulse 70; continued slow, in good health.	Lived five years longer; died of fracture of leg.	Heart large, pale, thicken'd; atheroma of aortic and coronaries; basilar arteries dilated.
114	Flint. Amer. Pract., 1976, vol. xiii. p. 1.	M. 43	40—29—26	No abnormal cardiac sounds.	Epileptiform convulsions recurred.	.....	Pulse slow, probably years, weakness and palpitation;	During fits pulse accelerated; in intervals 24-36; improved.	
115	Hewan. Monthly Abstr. Med. Soc., Phila., 1874-75, p. 400.	...	24	.....	Never fit or fainted, bears cold well.	.....	Studied greatly; pulse 72, then 55; 8 years ago 24; rheumatic fever.	Later gout and rheumatic, pulse 68; fell to 32 and 38 where it remained; could climb mountains.	
116	Regnard. Thèse de Paris.	M. 76	21—22	Murmur with first sound; reg.; "gr. silence," much prolonged; heart large.	.....	.....	Entered hosp. for hydrocele; had noticed a little oppression and less strength in legs; syncope; edema.	Left hospital.	
117	Prentiss. Trans. Amer. Physicians, vol. iv.	F. 75	35	Radial and heart correspond.	Attacks of faintness and vertigo, may have unconsciousness.	.....	Present attack with nausea; dizziness, faintness.	Improved.	
118	Bolton. British Med. Journ., 1874, p. 611.	F. 66	Weaker beat, after strong. 26	Weaker beat, after strong.	Occasional fits and loss of consciousness.	.....	Anxiety.	Improved on good diet.	
119	Thornton. Clin. Soc. Trans., vol. viii p. 95.	F. 20	16—20	Sphyg.; double beat.	Epileptiform; pallor.	.....	Operation for syphilitic laryngitis; pulse 40.	Improved; pulse to 48.	
120	Regnard. Thèse de Paris.	M.	41—46	.....	Loss of consciousness.	.....	....	Gradual improvement, but after 12 days pulse still low.	
121	Norris, British Med. Journ., 1879, vol. ii. p. 886.	M. 68	26	Hypertrophy; slight mitral mur.; edema of ankles.	Syncope.	Albuminuria.			

THE PRODUCTION OF SARCOSPORIDIOSIS IN THE MOUSE BY FEEDING INFECTED MUSCULAR TISSUE.[1]

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SINCE the discovery of sporozoan parasites belonging to the order now known as *Sarcosporidia* in the muscle fibers of the house mouse by Miescher, in 1843, many other mammals, and not a few birds, have been found to harbor them. Some species, like the one described by Miescher, are quite conspicuous to the naked eye in the ultimate stage of development. Certain others, including those of swine, are microscopic. Those of cattle may be seen as barely visible whitish specks when situated beneath the endocardium. Some of the species found in birds are fairly conspicuous, as shown by the dimensions given by Stiles.[2]

The record of sarcosporidiosis in man is meagre and in part uncertain in value. Only two cases, one described by Kartulis[3] and one by Baraban and Saint Remy,[4] seem to be genuine. In those of Lindemann[5] and Rosenberg[6] the diagnosis must remain doubtful. The case of Kartulis was that of a Sudanese. An abscess had formed in the liver and had extended to the abdominal wall. The sarcosporidia cysts were found in considerable numbers both in the liver and in the

[1] Owing to unavoidable delays the illustrations for this paper could not be reproduced in time for the TRANSACTIONS. They will appear with the text in the current volume of the Journal of Experimental Medicine.

[2] On the Presence of Sarcosporidia in Birds. Bulletin No. 3, Bureau of Animal Industry, Washington, 1893.

[3] Zeitschrift f. Hygiene, 1893, xiii. p. 1.

[4] Bibliographie anatomique, 1894, p 79; Comptes-rend. Soc. Biol., 1894, p. 201.

[5] Deutsch Zeitschrift f. Staatsarzneikunde, 1868, n. F. xxvi. p. 326.

[6] Zeitschrift f. Hygiene, 1892, xi. p. 435.

periphery of the abscess.[1] Baraban and Saint Remy found genuine sarcosporidia cysts in the muscular fibers of the vocal cords of an executed criminal. The cysts, from 0.077 mm. to 0.168 mm. in diameter, were chambered, and each chamber filled with falciform bodies or sporozoites. These two cases indicate that some one or more of the muscle parasites of the lower animals may reach maturity in the human subject.

This brief epitome of sarcosporidiosis in man leaves to this subject but little that is of immediate practical importance to human pathology. It should not be forgotten, however, that the muscular system in man is not subjected to that scrutiny which the viscera undergo in pathologic inquiries, and that sarcosporidia may be present and yet not be recognized. As in trichinosis, the invasion may be overlooked or the attending symptoms misinterpreted, and the subsequent quiescent stage fail to arouse any attention. The fact that the etiology of acute primary polymyositis is still unsettled should lead to more careful examination of the muscular system as a part of pathologic routine work. It is not improbable that invasion of the muscular system by aberrant parasites may take place now and then. Such parasites being in the wrong host may fail to develop, and hence elude detection, while the products resulting from their disintegration may lead to inflammatory reaction.

The supposition that sarcosporidia are transmitted by way of the digestive tract has been a favorite theory of investigators, and has been frequently tested by feeding infected muscle. No positive results have been reported. The failures were, no doubt, in part at least, due to the method of experimentation. The endeavor to transmit the sarcosporidia of sheep by injecting them into white mice and guinea-pigs, as was done by Kasparek,[2] or by the eating of raw meat by human beings, as was done by Moulé, seems at best abortive, since these parasites are highly specialized forms. It is, *a priori*, not improbable that the same species of sarcosporidia may infect several hosts possessing certain, to us unknown, relationships, but to gain an insight into the life-history of such forms the problem to be solved

[1] Max Braun, in reviewing this case, did not hesitate to regard the diagnosis of sarcosporidiosis as extremely doubtful, but he subsequently fully agreed with Kartulis after having examined the latter's preparations. Centralblatt f. Bacteriol., xviii. p. 13.

[2] Centralblatt f. Bacteriol., 1895, xviii. p. 327.

first is to determine the mode of transmission in the same species in which they naturally occur.

The negative results of transmission experiments on record, to which we may safely add many unpublished ones, induced me to make an effort to fill at least a portion of the existing gap, when, in 1898, I found a large proportion of gray mice which had been kept in a large wooden cage for over a year infected with sarcosporidia. The large number of infections suggested that transmission occurred directly and not through an intermediate host. The occasional discovery of dead mice in this cage, of which parts had been consumed, as well as the not infrequent mutilation of the tails and scrota of living mice, led to the hypothesis referred to above, that the infection takes place through the digestive tract in a manner analogous to the transmission of trichinæ. Though the experiments needed to demonstrate the truth or falsity of this hypothesis seemed at first simple and easily executed, yet in the course of carrying them out a number of factors appeared which had to be taken into account. The length of time consumed by each feeding experiment, about three months, permitted the introduction of the new control factors only slowly, so that these tests have extended over a period of more than two years.

In order to present the more important facts of these investigations in an intelligible manner, I shall first relate the life-history of the muscle parasite as interpreted by the results obtained. I shall then give such details of the actual experiments as may be necessary to enable others to estimate their relative value in establishing the results claimed, and to repeat them if thought desirable.

SARCOCYSTIS MURIS (R. Blanchard), Labbé.[1]

(*Miescheria muris.* R. Blanch., 1885.)

The parasite, as a rule, is noticed only in its matured state when it becomes visible to the naked eye. It seems to be pretty widely disseminated, and infected mice are encountered at intervals in most laboratories where mice are kept, to judge from verbal accounts of such discoveries in this country. The frequency with which they

[1] Das Tierreich. Sporozoa, Berlin, 1899, p. 119.

are found in rooms whither mice are drawn by ample food supply and where they breed is discussed in a subsequent section of this paper.

A mouse whose muscular system contains matured parasites presents a very striking appearance. If the skin be removed all the skeletal muscles will be seen to contain streaks of a whitish color. These may be so numerous as to leave but little of the normal red color of the muscle, or they may be quite scarce. Even the muscles of the head and the diaphragm are invaded. I have found them in sections of the eye muscles. The heart muscle, however, remains free. These linear streaks run parallel to the muscle fibers. In case of superimposed translucent layers whose fibers run in different directions, as in the abdominal muscles, the streaks are seen crossing one another at different angles. They vary more or less in length, the oldest and largest being from 1 to 1.5 cm. long and about 0.25 mm. broad. The more isolated ones are of greater width than those crowded together.[1]

If a piece of fresh muscle be teased in some indifferent fluid and examined under a low power the whitish streaks resolve themselves into opaque thin-walled tubes densely packed with crescentic bodies, the so-called sporozoites.[2] The outer wall of such a tube is very thin, smooth, and without any external appendages. It is usually encased by a narrow rim of muscle fibrillæ, the remains of the invaded fiber. Within this parasitic tube, among the sporozoites, a faint network of lines is discernible, which forms flattened meshes, whose long axes are at right-angles to that of the parasite itself. These are optic sections of partitions which divide the entire parasite into chambers which enclose the sporozoites. When the parasite is torn by teasing the latter escape and are found isolated. In outline they are crescentic and resemble bananas. The body in the middle is 0.004 mm. thick, and measures in a straight line from end to end 0.012 mm. A modicum of fine granules is recognizable, but nothing more.

[1] According to investigations made by Mrs. Gage (The Microscope, 1888, viii. p. 225) some of the fibers in the shorter muscles of the mouse extend from tendon to tendon. In the larger muscles they are, as a rule, shorter than the muscle itself. Exact measurements of isolated fibers showed a variation in length of from 5 mm. in the short muscles to 22 mm. in the longest muscles. I have not made any measurements upon isolated invaded fibers, but all observations point to the inference that the parasite eventually occupies the entire length of the muscle fiber in which it happens to lodge.

[2] The terminology used in this article is that suggested by Schaudinn. (See Lühe's review, in Centralblatt f. Bakt., 1900, xxvii p. 367.)

When these sporozoites, suspended in normal salt solution, are warmed to 35° or 37° C., they exhibit peculiar movements. These are better observed in slide cells with convex bottom than in the hanging-drop. By melting down the corners of square cover-glasses, as recommended by Siedlecki, good cells may be improvised with ordinary slides. The cells must be sealed with vaseline to prevent the concentration of the salt solution. The observations are most satisfactorily made with the aid of a Nuttall thermostat, into which the entire microscope is placed.

It will be noticed as the temperature rises that these bodies have become more homogeneous and somewhat refractive, and that their form has become slightly altered. They are now more curved and somewhat more slender. At 34° to 36° C. they begin to begin to move in a gliding manner on a circumference corresponding to their own curvature for from 1½ to 2 revolutions. Then they suddenly flop over—*i. e.*, revolve on their long axis ¼ to ½ a revolution. After from fifteen to thirty seconds of rest they pass through the same motions anew. Flagella were not observed. These movements may be observed for several hours. During the second hour they grew less and less vigorous, and finally only a few remained active. They are dependent on warmth, ceasing when the slide is removed from the thermostat or allowed to cool, and beginning again when it is warmed. I have seen a few move in midsummer in a temperature of 85° F. In the only experiment made to test the vitality of the sporozoites after the death of the host, they retained their power to move for at least four days, the mouse tissues being kept in the refrigerator in the meantime and examined from day to day.[1]

These observations lead to the inference that the sporozoites, owing to their perishable nature, must enter another host, presumably warm-blooded. The movements simulate a boring or screw-like action, which may come into play when they penetrate the mucosa.

When muscular tissue containing the matured sporozoites was fed to mice no evidence of any invasion of the muscle fibers was obtained until approximately the forty-fifth day, when the smallest parasites

[1] In some notes made in 1890, when this parasite came under my observation in a single case (Washington, D. C.), the same peculiar movements are recorded. The sporozoites of the sarcosporidium of sheep are described by L. Pfeiffer (Die Protozoen als Krankheitserreger, 1891, p. 123) as becoming ameboid when warmed in human saliva.

were first detected. The youngest parasite which I have recognized in fresh tissue was a fusiform body 0.152 mm. long and 0.02 mm. broad. This stage consists of a delicate structureless membrane whose contents, in the fresh condition, are hyaline and practically invisible. A moderate number of minute, scattering, refringent granules appear in its substance, which are of substantial aid in finding it.

In somewhat later stages, when the parasite has grown much longer, its substance is found divided into a number of broadly fusiform bodies, whose long axes are nearly parallel to that of the mother tube. In this stage the parasite readily slips out of the muscular fiber in which it is lodged when the fresh tissue is teased. It suggests a tube densely packed with small fish. These primary divisions of the parasite are 0.012 mm. long and 0.004 mm. broad in the middle. Each is provided with a spheric highly refringent granule 0.001 mm. in diameter, blackening slowly in osmic acid. It is contained in a minute vesicle. Beyond this the fusiform bodies reveal no structural details. Individuals are now and then found in which the division, completed in some parts, lags behind in others. The bluntly rounded ends of the parasite are usually behind the rest of the body in this respect.

This primary stage of the fusiform bodies is followed by another, seen first in the central portion of the tube. Here the parasite becomes broader and more opaque, owing to the presence of closely-packed crescentic or kidney-shaped bodies. Just what change takes place in the fusiform bodies which leads to the crescents I am unable to state. Certain appearances suggested a longitudinal cleavage of the former. One parasite in this transitional stage I was fortunate enough to obtain by teasing, completely freed from its encasing fiber. It was about 4 mm. long and 0.026 mm. broad.

In about seventy days after feeding the parasites enter the stage of spore and sporozoite formation. The substance of the parasite is now found to be made up of relatively large roundish or polyhedral masses of a finely-granular appearance, which are in close apposition with one another and 0.014 mm. to 0.016 mm. in diameter. These sporoblasts soon break up into the final sporozoites, the exact number of which I have been unable to determine. Probably eight are formed from each sporoblast. The continuous growth and breaking up of

the sporoblasts cause enough internal pressure to force the sporocysts to assume a flattened outline within the parent tube with their long diameter at right angles to that of the latter. The whole suggests the appearance presented by dried figs in their original package. The stage of the unsegmented sporoblast I have rarely seen, and I think it is of short duration, the sporocysts following closely upon this stage. Rarely in the same individual sporoblasts and sporocysts are found in different sections of the same individual at the same time. As stated above, the ripe sporozoites readily escape from the parasitic tube when fresh tissue is teased. This is not true, however, of any of the preceding stages. Neither the fusiform nor the succeeding crescentic bodies leave the parent tube when the latter is torn unless decomposition has set in or a 1 per cent. solution of acetic acid be added.

The account given above implies that the partitions within the sarcosporidium are not ingrowths from the external wall, as is frequently claimed, but that they are simply the walls of the sporocysts in close apposition to one another. I have seen nothing in my observations that would lead me to accept any other view with reference to the species under consideration.

Sarcocystis muris thus ripens within the muscular tissue in two and one-half to three months after the date of feeding. Ingestion of the infected muscle at this final stage by another mouse is followed by a similar infection of the muscular system.

It was not my purpose at this time to enter into any study of the morphologic details of the various stages in the intramuscular life of this sporozoon. It seemed, however, desirable to confirm the observations made with fresh tissues upon such as were fixed and hardened and stained according to current methods. In doing this the following plan was adopted:

Muscular tissue from chloroformed mice was fixed for twenty-four hours in Zenker's fluid, and then, after thorough washing, was hardened in ascending strengths of alcohol. The tissues were embedded in paraffin, after passing through cedar oil, and cut in ribbons. Various stains were employed, such as the various hematoxylin preparations, with or without eosin and picro-acid fuchsin; also eosin and Unna's polychrome methylene blue, and Heidenhain's iron hematoxylin. The best stain I found to be hematein-ammonium, which

I had prepared myself, and which stained rather slowly, and chiefly nuclear matter.

In the earliest intramuscular stages of the parasite seen a multiple division of the nucleus was already under way. The entire substance was mapped out into a large number of areas having certain definite characters. Each area consisted of a rather dense nuclear body 0.002 mm. in diameter, and with faintly lobulated periphery occupying a clear space two to three times its diameter. Within this space, and at a somewhat variable distance from the nucleus, was another body, perfectly spheric, about 0.0005 mm. in diameter, and staining compactly with chromatin dyes. The significance of this minute satellite accompanying each nucleus must be left to future cytologic studies.[1] All that I can state now is its unvarying presence in this early stage. It has not been described by Bertram,[2] who has studied the early stages of other species of sarcosporidia.

A division into separate individuals or cells was not noticed in the earliest stages. Somewhat later fusiform bodies appear in outline, each of which contains the nucleus and the micronucleus or karyosome above mentioned. The latter, however, soon disappears.

Beyond this the study of stained sections has not thus far contributed anything material to the facts brought out by the study of fresh tissue. No clue concerning the suspected division of the fusiform bodies before they enlarge into the sporoblasts was obtained. Nor did the examination of sections from a number of cases reveal the processes in the sporoblasts which end in the breaking up of these into sporozoites. Evidently these changes go on very rapidly and are encountered only through lucky accidents rather than carefully planned and executed experiments.

This fragmentary statement of what seem to be the stages leading to the formation of the sporozoites has been introduced simply as a stimulus to a more thorough study of this parasite, which feeding experiments enable us now to obtain in any desired amount. The statements of other observers point to a similar complex development of other members of this genus. Thus Bertram,[3] in a study of the sarcosporidia of sheep, speaks of the earliest divisions or cells as mother

[1] For similar bodies in the development of trypanosomes of gray rats, see Rabinowitsch and Kempner, Zeitschr. f. Hygiene, 1899, xxx. p. 251.

[2] Zool. Jahrb. Abtheilung f. Anat. u. Ont., v.

[3] Loc. cit.

sporoblasts, implying thereby a further division before the stage of sporoblast is reached. L. Pfeiffer[1] thinks that there may be crescentic bodies of the second generation, third generation, etc.

Experimental Data and Results.

Since the experiments the results of which I have briefly given are the first in which feeding has been successful, it is necessary to go somewhat into detail concerning the experiments themselves in order to point out the difficulties and limitations inherent in work of this kind to which bacteriologic methods are inapplicable. The details which require special attention are: (1) The source of the animals used; (2) the association of the animals with one another in confinement; (3) the food; (4) the ectoparasites of mice, and (5) the method of feeding the infected material.

1. The common gray house-mouse was used almost exclusively. A few white mice and crosses were included, and the results indicated equal capacity for infection. Since it is impossible to tell, without removing bits of muscular tissue by a surgical operation, whether any mouse is infected spontaneously, even a severe infection being compatible for many months with a sleek appearance and the usual vivacity, control observations were made upon mice during the whole period of the investigation. The surgical operation referred to was considered inapplicable in the case of such small animals, not to mention the chances for missing slight infections. The chief source of the mice was a room where the small laboratory animals were kept. Mice caught in this room as well as elsewhere were examined microscopically. Portions of muscular tissue were teased fresh in normal salt solution and carefully scrutinized with the 16 mm. and 4 mm. objectives for those earlier stages which are not visible to the naked eye. One hundred and fifty-five control mice, of which 120 were from the animal-room above referred to, were examined in this way. Of the 35 from outside sources 1 was found infected. Of the 120 from the animal-room examined over a period of three years, 8, or about 6⅔ per cent., were found infected.

This rather high rate of infection is probably due to the fact that before attention had been directed, in the spring of 1898, to the in-

[1] Die Protozoen als Krankheitserreger. Jena, 1891, p. 119.

fected cage a mouse may have occasionally escaped from it and carried the infection into the hiding places. A tabulation of all the facts bearing upon these control mice showed that there was a slight wave of infection during the winter months of both 1900 and 1901, which, judging from the age of the sarcosporidia, started near the beginning of December. It was almost wholly confined to the large adults, male and female, and was most probably due to some old mouse killed and partly consumed by others.

2. The association of mice in confinement may lead to general infection if a spontaneously diseased mouse should die in the cage. In order to eliminate this source of error the mice were either transferred directly to glass jars, one or two in a jar, or else when they were stored in cages in larger numbers, any that died or were removed for other purposes were carefully examined.

3. The food of the mice was at first bread and oats, later oats almost exclusively. The possibility that the oats might be contaminated led to steaming them before use. The general outcome of the experiments does not favor the hypothesis that infection may occur in this way. The bedding for the jars was carefully selected from hay and straw, and in the later experiments sterilized dry as a final precaution.

4. The negative outcome of the feeding experiments of former observers, taken together with the somewhat unexpected results of investigations upon other protozoa which demonstrated that arachnids are the transmitters of bovine malaria (Texas fever), mosquitoes of human malaria, that flagellates in the blood of rats are transmitted by fleas, in the blood of larger animals by a fly (*Glossina morsitans*), made it necessary to examine any possible relationship between sarcosporidiosis in mice and certain ectoparasites which infest them. There is, however, no close analogy between the transmission of micro-organisms circulating freely in the peripheral capillaries and such parasites as are situated more deeply and securely in the muscle fibers. The ectoparasites of the mice which came under my observation were two species of mites, *Myobia musculus* and *Myocoptes musculinus*. They were either found on different animals at different times or else associated together on the same individual. In order to bring them into view the skin of the chloroformed mouse was left from a few to twenty-four hours under a bell-glass. Any mites would then appear on the hairs, usually near the tips. *Myocoptes* was first

encountered as a delicate woolly scab around the base of the ears. In this colonies of eggs and immature young were found. More rarely colonies of young were found in the subcutis as round, flat masses not more than 1 mm. in diameter and resembling a little bit of circumscribed adipose tissue. Adult *Myocoptes* were occasionally found in large numbers on unthrifty caged mice. As a rule, mice confined together in numbers up to 15 or 20 were infested.

The possible relation of these mites to the sarcosporidia was carefully taken into consideration by noting their presence or absence on the animals examined. As they are very small, and cannot be made out distinctly without a hand lens, they may be overlooked when very few are present.[1] They did not seem to bear any etiologic relation to the muscle parasite. They were frequently noted as absent in positive cases and very numerous in negative cases. Long cohabitation with infected mice in the presence of these mites did not increase the opportunity for infection, as will be pointed out farther on.

5. As stated above, the mice used in the experiments were either kept before the feeding in lots of ten to fifteen in large cages made of wood and fine-meshed wire, or else they were placed directly into glass jars. Ordinary battery jars, six by eight inches, were covered with a galvanized iron wire top, with meshes too small to admit houseflies. From this top a small glass dish to hold water was suspended with copper wire. The drinking water was renewed by removing the wire top and slipping a glass plate in its place temporarily. The drinking dish left attached to the wire top was rinsed and filled and the top replaced. This arrangement kept the bedding dry, and the jars were changed but once in three weeks. The grain was poured into the jar, and the hulls slowly accumulating were removed when the jar was changed. In such jars two, very rarely three, were kept.

In experiments from No. 8 to No. 19 the infection of the mice was effected in the following manner: Food was usually withheld for the day, and toward evening the muscular tissue of the infected mouse, freed completely of skin and entrails, was cut up into fine bits in normal salt solution. This mass was mixed with bread crumbs in a small glass dish and moistened, if necessary, with more salt solution.

[1] *Myobia* is about 0.5 mm. long and 0.2 mm. broad. *Myocoptes* is about 0.3 mm. long and 0.13 mm. broad. These dimensions apply only to adults.

Each jar, containing one or two mice, received a dish. The amount eaten was noted next morning. In the earlier experiments the muscular tissue or a piece of the carcass was placed in the jar without any preparation, but the mice often refused to touch it. The food substances mixed with the infected flesh must be properly chosen. I have found bread crumbs softened in normal salt solution a favorite dish. In the summer of 1900 I used corn meal, but the mice threw it out of the dishes, and I attribute the failure of certain experiments to the injudicious selection of the food. The mice to be examined were usually chloroformed, more rarely killed by a blow while under chloroform. The latter did not affect the vitality of the sarcosporidia or of the mites.

When the preliminary experiments had made it evident that the sarcosporidia enter the muscles by way of the digestive tract, it became necessary to determine the time after feeding when the parasites begin to appear in the muscle fibers, or can be recognized therein, and the time required for the ripening of the sporozoites. In order to eliminate errors of interpretation it was desirable to examine the animals during the earlier, most characteristic stage of the muscle parasite, because the later ripe stage remains unchanged indefinitely and gives no clear testimony concerning the probable date of infection. To determine the time of the earliest appearance of the parasite in the muscle fiber, infected mice were killed at different periods after the feeding, and the quite uniform answer given by all experiments was that the earliest stages were detected between the fortieth and the fiftieth day after feeding.

The table given below has been condensed from one upon which all the details of the experiments to which any attention has been given were noted. Among these are the source, size, and sex of each mouse, the date of capture, the mode of confinement, and the presence or absence of mites. A study of these data led me to regard most of them as negligible factors, and they are, therefore, omitted from the published table.

In the examination of the mice a careful record was kept of the stage of development of the muscle parasite, and upon this record is based the number of cases which are put down as the result of artificial infection and the number in which the infection had presumably occurred in the natural way.

No. of experiment.	No. of mice used.	Source of mice. Animal room.	Source of mice. Elsewhere.	Date of feeding.	Manner of feeding.	Mice examined: Before 45 days after feeding. Infect'd	Before 45 days after feeding. Not infect'd	Between 45 and 60 days after feeding. Infect'd	Between 45 and 60 days after feeding. Not infect'd	Later than 60 days after feeding. Infect'd	Later than 60 days after feeding. Not infect'd	No. evidently infect'd spontaneously.	No. infect'd by feeding	Source of infected muscle.
1	1	...	1	Nov. 18, 1898	Portion of body of infected mouse.	0	1							
2	2	1	1	Jan. 4, 1899	" " " "	1	1	...	...	...	...	1		
3	4	?	?	Feb. 1, "	" " " "	0	4							
4	4	?	?	Feb. 24, "	" " " "	...	...	...	...	1	3	...	1	
5	2	?	?	May 20, "	" " " "	...	...	...	...	2	0	...	2	
6	2	?	?	May 22, "	" " " "	...	...	...	..	1	1	...	1	
7	6	?	?	Sept. 15, "	" " " "	0	4	...	...	1	1	...	1	Exp. No. 6.
8 *a*	8	Animal room.	...	Oct. 3, "	" " " "	0	4	2	0	2	0	...	4	
8 *b*	6	"	...	Oct. 3, "	Muscular tissue and bread and salt solution.	1	1	4	0	...	...	...	4	Exp. No. 5.
9	11	" & elsewh	...	Dec. 9, "	Muscular tissue and bread and salt solution.	0	7	2	0	1	1	1	2	Exp. No. 8.
10	7	1(?)	6	Jan. 15, 1900	Muscular tissue and corn meal and salt solution.	0	1	2	1	2	1	1	3	Infected cage.
11	4	3	1	Feb. 22, "	Muscular tissue and corn meal and salt solution.	1	0	3	0	...	...	1	3	Infected cage.
12	2	...	2	Mar. 28, "	Muscular tissue and bread and salt solution.	...	...	2	0	...	...	...	2	Exp. No. 10.
13	12	9	3	May 9, "	Muscular tissue and corn meal and salt solution.	...	...	4	2	2	4	...	6	Infected cage.
14	18	18	...	June 26, "	Muscular tissue and corn meal and salt solution.	0	6	1	2	2	7	...	3	Infected cage.
15	2	...	2	Aug. 25, "	Muscular tissue and bread and salt solution.	...	..	1	0	0	1	...	1	Exp. No. 13.
16	10	...	10	Sept. 19, "	" " " " " "	0	1	...	...	7	2	1	6	Exp. No. 14.
17	8	4	4	Nov. 25, "	" " " " " "	0	1	...	...	5	2	...	5	Infect. cage.
18	17	11	6	Dec. 18, "	" " " " " "	0	9	...	...	6	2	...	6	Exp. No. 16.
19	8	...	8	Mar. 23, 1901	" " " " " "	...	...	6	2	...	...	...	6	Exp. No. 17.
					Totals . . .	3	40	27	7	32	25	6	56	

Before discussing the results of the experiments as a whole, a few remarks concerning some of them may not come amiss. One of the earliest (No. 2) led me to assume erroneously that the parasite appears very soon—within a week—in the muscular tissue. Six days after the single mouse had been fed it died, and in the abdominal muscles were found the earliest segmenting stages of the parasite. Later experiments made it evident that the mouse was infected when used. Somewhat later the feeding experiments made with the carcass of infected mice yielded results which seemed to point to wound infection. Those fed with bony portions were found more frequently infected. This inference was also found to be an error, and was given up when the feeding of bread with the infected muscle proved so successful. Of the later experiments, No. 12 deserves notice. The two mice which were caught in a distant building and did not come in contact with any others were both found in the earliest stage of infection on the fifty-first day. Experiments Nos. 13 and 14 yielded very poor results, yet these were offset by the fact that there was no evidence that any mouse had been infected before use. The partial failure to infect I attribute, as already stated, to the use of corn meal. On several occasions I have noticed that mice recently caught in distant buildings were less inclined to eat the infected food than those caught in the animal-room or confined for some time in cages or jars where food was always plentiful. Possibly the changed environment leads to a more voracious appetite, which may influence the results of experiments. In not a few instances only one of two mice fed together in the same jar was found infected.

Before leaving the subject of minor details I shall give an account of Experiment No. 18, which may be taken as a type of the later ones. In this eighteen mice were used, of which one was found dead in the course of the experiment, but too late to be examined, leaving seventeen; eleven of these were from three cages stocked during the summer of 1900. Control examinations of all that died in the cages were made. Two were from a distant house, placed together in a jar, four were white mice raised in another house, also kept by themselves. On the day of feeding the eleven gray mice had been confined for three to four months, and were not very thrifty. Of these nine were chloroformed from two to forty-one days after feeding, but no infection detected. The remaining two were exam-

ined on the sixtieth and sixty-second days respectively, and the infection found in the early stages. The two gray mice from a distant house, confined only two days before feeding, refused the infected food. Both were found free from infection on the ninety-fourth day. The four white mice were examined sixty-seven, sixty-nine, and eighty-five days after feeding, and were found in stages of infection corresponding to the assumed cycle of development of the parasite. Both negative and positive cases were infested with mites.

In No. 19 all the mice were from a distant house and kept separate from those caught in the animal-room. There were four jars, containing two apiece. Between the fiftieth and sixtieth day all were chloroformed; six out of eight were in the earliest stages of sarcosporidiosis. In two jars both mice were affected; in the remaining two only one each. A fifth pair of mice from the same source, and kept with these in the same way as controls, were killed at the same time. Both were free from infection.

Turning to the results of these experiments, we find that of the 43 mice killed before the forty-fifth day 3 were infected. On account of the advanced stage of the parasites, these are classed as infected before use. Of the 34 killed between the forty-fifth and sixtieth day 27 were infected. Of these, 1 is classed with the spontaneous infections. Of the 57 killed after sixty days 32 were infected. Of these, 2 are rejected as previously infected. Taking all together, we have of 91 examined after forty-five days, 59 infected, 32 not. Rejecting 3 of these, we have an infection of 63.6 per cent. after forty-five days. If we compare the spontaneous infections discovered in the experimental mice with those of the mice examined as controls we find a close agreement. Eliminating from both series all mice caught outside of the animal-room we find the control series of 120 mice from the animal-room yielding a spontaneous infection of $6\frac{2}{3}$ per cent.; the experimental series, of $6\frac{2}{3}$ per cent. also, if we include in this series all mice whose source is indicated as doubtful in the table, which would make 90 in all. It is highly probable that all mice marked doubtful came from the animal-room.

It is of interest to compare with these statistics those of the permanently infected cage. When the disease was first discovered it was thought that simple cohabitation might induce it, and hence fresh mice were introduced from time to time. To make sure of the per-

sistence of the infection the bodies of infected mice were placed in the cage temporarily from time to time. In February, 1900, a jar containing bits of infected muscular tissue mixed with bread crumbs was put into the cage. Seventy-six days later 6 out of the remaining 10 mice were found infected. Four were in the earlier stages, suggesting the last feeding as the cause; 2 were in advanced stages. Whether they were also infected with younger stages was not noted. Of the 39 mice taken from this cage of which I have any records, 19 were infected, 20 free, yet all had been in the cage from six to twelve months and continuously exposed to mites and fecal discharges, and all had had an opportunity to infect themselves by feeding. Under these conditions about 50 per cent. became diseased, whereas in the feeding experiments the net positive result is 63.6 per cent.

The life-history of *Sarcocystis muris*, as interpreted by the results of the foregoing experiments, consists in the invasion of the muscular system of the mouse by sporozoites taken in with the food. The sporozoites, being contained in cysts, cannot escape, and the infection can take place only when muscular tissue is eaten. The long period between infection and the growth of the parasites in the muscle fibers might be interpreted in two ways:

1. The parasite requires a long time to store up enough energy to undergo the rapid growth and multiple division of the nucleus terminating in the formation of spores and sporozoites. Similarly long periods are required by the various cysticerci of the common tapeworms of man to reach the—for them—mature stage.

2. The sporozoites after ingestion develop into sexually mature organisms in some part of the body in a manner analogous to the genus *Coccidium*. After fertilization the female organism (macrogamete) migrates into the muscle fibers and there passes through the process of sporogony.

This second hypothesis seemed the more attractive one at the outset, and much time was devoted to tracing the hypothetic sexual elements in various organs of the body. Especially the intestinal tract was scrutinized carefully in animals killed at stated intervals after infection. The intestinal contents, the epithelium, and the submucosa were searched in fresh preparations, in some cases in sections, for any forms which might be taken for the parasites sought for. The fate of the sporozoites soon after feeding was investigated, but no traces of

them found. The spleen, kidneys, and the bone-marrow as well as the blood received attention, but nothing definite was discovered.[1]

Another view suggested itself as an outgrowth of the second. It was assumed that the sporozoites became sexually mature in the intestines, were discharged, and then ingested either by the same host or other mice. This hypothesis was discredited by the impossibility of producing the disease by simple cohabitation in infected cages. Yet the occasional discovery of minute coccidia-like bodies in the intestinal contents led to a more thorough search, without, however, leading to any result. The following experiment was also made: Two white mice from Experiment 18, kept together in the same jar, were transferred to fresh jars on the second, third, fourth, sixth, eighth, ninth, and eleventh day after feeding, to remove any hypothetic sexually mature elements discharged with the feces. The mice were nevertheless found severely infected in due time.[2]

My observations have thus not yet bridged the gap up to the sixth week. Careful examinations of the fresh muscular tissue of mice killed earlier than this have been made in large numbers, but they are not sufficient in themselves to warrant the assumption that the immigrated sporozoite is not present much earlier than this. The examination of stained sections in considerable numbers will be necessary. It may be found that the parasite reaches the muscle fiber soon after ingestion, where it remains undetected until the multiple division of the nucleus begins and the organism, by its rapid growth and increased affinity for chromatin dyes, becomes recognizable. One parasite which was found fifty-one days after feeding measured only 0.05 mm. in length and 0.016 mm. at its greatest width. These dimensions are four times those of the sporozoite—a very slight increase in this long period of time.

There are several aspects of this whole subject which have suggested themselves in the course of the investigation and which I shall touch upon very briefly.

The infected tissue used for feeding came, in about one-half of the experiments, from mice taken from the infected cage. In the other

[1] In the spleen I encountered quite regularly the large giant cells of the bone-marrow.

[2] In the digestive tract of many mice kept confined for some months and not very thrifty, two flagellates, *Lamblia intestinalis* and a trichomonas-like form, were frequently encountered in the small intestine, together with an ameba in the cecum. These protozoa it was believed bear no genetic relation to *Sarcocystis muris*.

half mice from one of the preceding experiments were used as indicated in the table. In the later experiments it became evident that the sarcosporidia developed somewhat more slowly than in the earlier, and that the fully matured muscle parasites were smaller than in the earlier and in the spontaneous infections, due not to any shrinkage in size of the sporozoites, but to a smaller number. This apparent degeneration may be due to the feeding of tissue from artificial infections—a kind of artificial cultivation of the parasite under slightly abnormal conditions, such as monotonous diet and confinement of the host. It may also be due to the need of passing temporarily to some other host, or perhaps to other still unknown causes.

Can mice be infected twice or oftener, or does the first feeding establish immunity? This question was approached in one experiment. Two mice in Experiment 17, fed November 25, 1900, were fed again after fifty-five days, on January 19, 1901. They were killed March 22, about four months after the first, two months after the second feeding. There was an abundant invasion due to the first feeding, but none traceable to the second feeding. Simultaneous feeding of other mice on January 19th was successful.

Another question which has an important bearing on the outcome of feeding experiments is that of an initial immunity which may lead to a destruction of the sporozoites before they reach the protecting envelope of the muscular fiber. That such immunity exists is suggested, but not demonstrated, by the general outcome of the investigation. I have already referred to the disinclination of recently caught mice to eat muscular tissue mixed with bread, but this only partly explains the results.

May sporozoites infect when injected into the subcutis or the abdominal cavity? With the earlier feeding experiments five separate tests were made to solve this problem. The results, though leaning decidedly toward the negative, were not quite satisfactory and will have to be repeated on a larger scale.

I have left the chapter on the pathology of sarcosporidiosis in the mouse as well as the toxicity of the sporozoites, as brought out by L. Pfeiffer[1] for the parasite in sheep, and subsequently by Laveran and Mesnil[2] for the same species, for special consideration. In general

[1] Loc. cit., p. 123

[2] C. R. Soc. Biol., 1899, p. 311.

the tissue reaction appears to be very slight during the developmental period of the parasite. Multiplication of muscle nuclei, scattering, small foci of leukocyte infiltration associated with slight cell proliferation of the perimysium internum and the sheath of the small vessels are usually present, but they apparently stand in no direct relation to the invasion for the infected fiber, and its immediate environment are in nearly every case normal. To interpret the slight changes present the condition of the muscular tissue preceding visible invasion will need special attention. When the parasites are very large and numerous disturbances in the movements of the animal should occur, and as a matter of fact such mice are frequently found slow in movement and ill. The sporozoites in the old cysts may shrivel and disappear and leave the chambered cysts empty. In one case I found them filled with polymorphonuclear leukocytes.

The life-histories of all sarcosporidia are not necessarily explained by the results obtained with *Sarcocystis muris*. It would be difficult, for instance, to account for the sarcosporidia of cattle in the way those of mice can now be accounted for, since cattle are not carnivorous. Their muscle parasite is either an aberrant form of some invertebrate taken in with their food, or else there is an intestinal stage as well which readily permits a discharge of spores outward. It is obvious that other views or modifications of the views presented might be brought forward, but I desist from any further discussion not based on actual studies.[1]

The experiments described in the foregoing pages warrant the conclusion that the feeding of *Sarcocystis muris* containing ripe, mobile sporozoites to gray and white mice is followed by an invasion of the muscle fibers which becomes readily recognizable after the forty-fifth day. At this time the parasite is, as a rule, many times larger than the sporozoite which it presumably represents. Within two and one-half to three months the parasite has reached the final stage, in which it consists of a chambered cyst filled with sporozoites, mobile at the temperature of the body and capable of infecting other mice.

[1] See a paper by the writer "On a Sporozoon in the Intestinal Villi of Cattle," in Bulletin No. 3 of the Bureau of Animal Industry, United States Department of Agriculture, 1893, p. 73.

THE ACID INTOXICATION OF DIABETES IN ITS RELATION TO PROGNOSIS.

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While the admirable studies of Stadelmann,[1] Naunyn,[2] Minkowski[3] and Magnus-Levy[4] have firmly established the fact that the peculiar coma so often noted in diabetes is regularly associated with the excretion of large quantities of organic acids, comparatively little attention has been devoted to the study of the excretion of such acids during the period preceding the onset of coma. I desire here to call attention to the appearance of organic acids in the urine previous to the actual development of coma, with a view to emphasizing their prognostic significance.

Methods of Detecting the Presence of Acids in the Urine.

In the cases to be reported here the chief method employed to determine the amount of organic acids excreted has been the process consisting in the estimation of the acids and bases of the urine. In health the urine contains four chief acids united to five different bases, and these acids and bases very nearly neutralize one another. In diabetes, on the contrary, the total known acids of the urine may fail to neutralize the total quantity of known bases, and there is an *apparent* excess of bases. The excess of bases over acids is only apparent, for the urine does not contain free alkali. The apparent excess of bases is in reality united to acids, but these acids are not the *known* acids referred to above; they are organic acids, and the apparent excess of bases is proportional to the quantity of organic acid which is being excreted. On the basis of these facts, which were first recognized by Stadelmann, Dr. A. J. Wakeman and I have de-

veloped a method[5] of estimating the organic acids of the urine, and this method has been used in our cases. It is of course to be understood that by this method we do not obtain any clue to the nature of the organic acids, but only a knowledge of their combining power. This knowledge enables us to express the amount of acid present in terms of oxybutyric or any other organic acid, and in reference to the quantity of acid excreted in our cases oxybutyric acid is chosen because it is the preponderating pathologic organic acid in cases of diabetes.

The quantity of NH_3 excreted serves roughly to indicate the extent of the excretion of the organic acids. This of course depends on the fact that ammonium is the base chiefly concerned with the removal of organic acids from the body. It is estimated that a daily output of 2 grams NH_3 corresponds to about 6 grams of oxybutyric acid, 5 grams NH_3 to about 20 grams, and 8 grams NH_3 to about 36 to 40 grams of oxybutyric acid, but I shall show later that a considerable amount of organic acid may exceptionally be excreted without the NH_3 output being above the normal. Nevertheless the method is a valuable one for clinical purposes. We have determined the NH_3 output as part of the process of balancing the acids and bases, but have seldom relied entirely upon it as our evidence of the excretion of organic acids.

In many instances the presence of oxybutyric acid has been ascertained by obtaining crotonic acid from the urine in the well-known manner. Little attention has been paid to diacetic acid, partly on account of its instability.

The Excretion of Organic Acids Shortly Before or During the Period of Coma.

Cases I. *and* II.

The urines from several diabetic patients in a state of coma have come under our observation. In the first patient, a young girl in the care of Dr. E. G. Janeway, the bases were so much in excess of the acids in a separate sample of 340 c.c. of urine that the urine was estimated to contain 27.17 grams of oxybutyric acid in the last twenty-four hours. In the second case, a woman brought comatose into the City Hospital, without a history, the excess of bases indicated the ex-

cretion of more than 10.80 grams of this acid in twenty-four hours. In the first case the N of NH_3 was 20.88 per cent. of the total N; in the second it was 16.73 per cent. of the total N. The second patient came to consciousness after an infusion of sodium bicarbonate, but soon lapsed again into coma. Autopsy showed no lesions which would explain coma except an atrophic pancreas, and the case was regarded as one of diacetic acid intoxication.

Case III.

A third case of diabetic coma from which the urine was obtained was in the surgical service of Dr. Markoe, in Bellevue Hospital. The small specimen of urine drawn from the bladder after the onset of coma contained 13.50 per cent. of N of NH_3, and the excess of bases indicated an amount of organic acid equal to 9 grams of oxybutyric acid calculated for twenty four hours, assuming an excretion of 10 grams of N in this period. This is doubtless an underestimate of the quantity of acid.

Case IV.

Beside these three cases of diabetic coma I have had under observation four cases in which coma appeared several weeks after the recognition of large quantities of organic acids in the urine. One of these was a patient of Dr. J. S. Ely, of New Haven. On February 26, 1901, the urine for the twenty-four hours contained organic acids equal to 25.96 grams of oxybutyric acid, and 20 per cent. of the N was present as N of NH_3. On March 20th (nearly four weeks later) the urine contained acids equal to 23.72 grams. of oxybutyric acid, and 21.28 per cent. of the N was present as N of NH_3. In the course of a few weeks this patient died in diabetic coma.

Case V.

The second observation relates to a man of thirty, a patient of Dr. H. P. Loomis, who is known to have had glycosuria for at least six months, and who had lost considerable weight when the urine was studied, November 1, 1900. On this occasion the excess of bases was equivalent to 24.62 grams of oxybutyric acid and 18.45 per cent. of the N existed as N of NH_3. Two weeks later this patient died in diabetic coma after a short period of drowsiness from which he was

temporarily roused by an intravenous alkaline infusion. All the urines from this patient that were examined yielded large amounts of crotonic acid.

Case VI.

Another case to be included in this category is that of a child, aged four years, in whom glycosuria was detected about one month before the time of our first analysis of the urine. This glycosuria followed the excessive use of sugars and starches, and was at first thought to be of alimentary origin. A twenty-four-hour specimen was obtained at a time when the child was on a diet moderately restricted as regards carbohydrates. This urine contained an amount of organic acid equal to 7.77 grams β-oxybutyric acid—a considerable quantity for a child of four years. Crotonic acid was obtained, but only in small amount. The N of NH_3 reached 19.57 per cent., and the total NH_3 was 1.46 grams. Ten days after the time of this analysis the child suffered from headache, and was given 2 grains of calomel. The sugar in the urine fell greatly when the calomel began to act, and a sample was obtained which showed only 0.031 per cent. of sugar as indicated by titration with Fehling's solution. The urine at the time of the previous examination had contained 4 per cent. of glucose (42 grams in twenty-four hours). An ammonia determination was made to see if there was a corresponding diminution in the excretion of organic acid. It was found that the NH_3 amounted to 2.51 grams when calculated for the twenty-four hours, and the N of NH_3 amounted to 28.11 per cent. These figures correspond to a large quantity of organic acid, and the observation is a striking example of the independence of the excretion of sugar and organic acids. This patient died in coma one month after the last observation mentioned. Diacetic acid was always present in the last month, and the acetone output was increased.

Case VII.

The last observation in this group relates to a distinguished scientist, aged fifty-two years, under the care of Dr. Osler, who had diabetes for at least ten years before he came under my observation. The percentage of glucose had gradually increased from 0.5 per cent. to 4 or 5 per cent. It cannot be said that the patient

exercised sufficient care in regard to the use of carbohydrates. In June, 1900, after a winter of hard work and worry, he began to have headaches at night and giddiness and diplopia during the day. There were also debility and irritability. These symptoms followed an indiscretion in diet. The urine for twenty-four hours, ending the morning of June 14 (during the disturbance) contained sugar, 5 per cent. (70 gm. in twenty-four hours), less than 0.4 gm. of organic acid (calculated as oxybutyric), 4.61 per cent. of N of NH_3, and only 0.66 gm. of NH_3. No test was made for acetone or diacetic acid.

On October 9th, after a summer of rest, from which there resulted a gain in weight and strength, the urine of this patient contained in glucose 4.46 per cent. (81.17 gm. in twenty-four hours), N of NH_3 3.62 per cent., and NH_3 0.629 gm. The organic acids of the urine amounted to 1.8 gm. in terms of oxybutyric acid. The increase in these acids was so small as to be considered of little prognostic significance. Nevertheless, the patient was urged to see Dr. Osler in the hope that he might be induced to take better care of himself. During the end of January, Dr. Osler wrote that our diabetic patient had what appeared to be an influenza infection with herpes of the first division of the fifth nerve. After losing much weight and strength there was a considerable recovery of weight and some recovery in strength, but after a short interval a boil developed on the leg, the patient became restless, vomited repeatedly, and soon died in deep coma. Dr. Futcher (to whom I am indebted for notes on the progress of the disease) states that there was a definite acetone odor to the breath and that the respiration became of a suggestive Küssmaul type. The following facts relative to the urine were given me by Dr. Futcher:

January 22, 1901. Specific gravity, 1033; sugar, 4.2 per cent. (polariscope). Amount of urine not stated. Legal's acetone reaction very marked. Typical Gerhardt's reaction for diacetic acid. β-oxybutyric acid, 0.2.

25*th*. Specific gravity, 1037; sugar, 4.6 per cent. Acetone and diacetic reaction marked. β-oxybutyric acid not tested for.

28*th*. Sugar, 7.9 per cent. Acetone and diacetic acid reactions just appreciable, and that is all.

February 17*th*. Sugar, 6.25 per cent. No diacetic acid or acetone reactions present.

The seven cases included in this group (of diabetic patients) agree in that they all show the presence in the urine of large amounts of organic acids. This was demonstrated in most instances by the method of balancing the acids and bases of the urine and by the less reliable but still satisfactory method of simply determining the NH_3 of the urine. In all the cases where an attempt was made to obtain crotonic acid it was found, and we can regard this as satisfactory evidence of the presence of oxybutyric acid in the urine. These results are in entire accordance with those obtained by Stadelmann, Naunyn, Minkowski, and Magnus-Levy from patients either actually in coma or a few days or weeks before the onset of coma. The excretion of acids is often greater before the period of actual coma, for the urine may be considerably decreased in volume at the time of unconsciousness. This was the case in the fourth observation, which has been elsewhere reported in detail by Dr. Ely.

The relatively short time that may elapse between an apparently stationary condition with little excretion of acid and a state of intoxication ending in coma is well seen in Case VII. Analyses made in June and October, 1900, showed the patient to be passing very little organic acid and to be gaining in weight and strength. Diacetic and oxybutyric acid appeared during an acute infection in January, 1901. During a short time the patient gained weight rapidly, and the reaction for diacetic acid could no longer be obtained. Then, after a new infection, diacetic acid reappeared and coma soon developed. Thus the patient died in diabetic coma only six months after the urine was carrying away very little organic acid.

I do not know of any observation on the urine of a patient in diabetic coma that has failed to show the presence of large amounts of organic acids. Our own results, taken in conjunction with those of Stadelmann, Naunyn, Magnus-Levy, and others, show that in diabetic coma and the antecedent period the N of NH_3 is increased to between 16 per cent. and 30 per cent. of the total N. In one of our cases a small portion of urine, representing only a part of the day's excretion, contained only 13.56 per cent. of N of NH_3, but it is likely that the average for a day would have been higher. In most instances of coma the N of NH_3 falls between 16 and 25 per cent. of the total N. The actual quantity of acid excreted varies enormously. If the kidneys are inactive the quantity may not exceed 10 or 12 gm. of

oxybutyric acid. On the other hand, Magnus-Levy mentions an instance in which the amount was 157 gm.

The increase in the excretion of NH_3 is satisfactorily explained on the hypothesis that this NH_3 is diverted from its usual conversion into urea, for the purpose of neutralizing the acid which is constantly leaving the cells to pass into the blood.*

Cases of Diabetes in which Considerable Quantities of Organic Acids were being Excreted, and which have not yet Developed Coma or in which the Outcome is Unknown.

Case VIII.

Perhaps the most instructive case in this group is that of a small and emaciated female, aged fifty-five years, in whom glycosuria had existed for about two years at the time of her admission to the City Hospital. The urine on October 13, 1900, contained organic acids equal to 13.15 gm. of oxybutyric acid and 16.34 per cent. of the total N existed as N of NH_3. The patient was at this time on a free diet containing a large amount of carbohydrates. The diet was restricted in carbohydrates, and on November 1st the urine contained 8.85 oxybutyric acid, with 11.55 per cent. of N as N of NH_3. Crotonic acid was readily obtained. Three weeks later, the diet remaining restricted as regards carbohydrates, the urine contained only 0.98 gm. of organic acid, while the N of NH_3 had fallen to 3.28 per cent. A specimen obtained so recently as March 27, 1901, shows less than 5 gm. of oxybutyric acid in twenty-four hours, and only 5 per cent. of N of NH_3. The recent urines have yielded only small amounts of crotonic acid.

The instructive features of these observations are, first, the fact that the patient had lived nearly seven months in spite of the fact that the urine contained so much organic acid as to call for 16.34 per cent. of N of NH_3 to aid in its neutralization, a percentage seldom observed except in patients on the verge of coma; and, second, the marked falling off in the organic acids which followed a moderate restriction in diet, and which has continued in spite of a more liberal

* This subject is discussed in the paper on the Pathology of Acid Intoxications in the Transactions of the Association of American Physicians, vol. xv., 1900.

diet latterly. The patient has become very much emaciated and is often somnolent during the day.

Case IX.

A similar observation was made on a corpulent man, aged forty-five years, who has had glycosuria for ten years. For many years the rigid exclusion of carbohydrates from the diet was promptly followed by the disappearance of sugar from the urine, but for more than a year the glycosuria has persisted in spite of the severest restriction in diet. On March 18th this patient passed 3700 c.c. of urine containing 4.7 per cent. of sugar and the equivalent of 9.26 gm. of oxybutyric acid. After four days on a restricted diet, 2380 c.c. of urine were passed with 2.75 per cent. of sugar and only 1 gm. of oxybutyric acid. Although the patient continued to live on a somewhat restricted diet, the acids increased to 10.7 gm. of oxybutyric acid in less than one week from the time of the previous observation. The first of the three urines mentioned yielded crotonic acid, and there is no doubt that at least part of the organic acid excreted consisted of oxybutyric acid.

It is of interest that no diacetic acid could be detected in the urine just mentioned, although the examination was promptly made.

An exceptional and highly noteworthy feature of this case is the behavior of the nitrogen of ammonia. The first analysis gave 2.42 per cent. of N of NH_3, with a total of 0.82 gm. of NH_3. The second analysis gave 3.27 per cent. of N of NH_3, with a total of 1.08 gm. of NH_3. The third analysis gave 4.14 per cent. of N of NH_3, with a total of 1.31 gm. of NH_3. These values all fall within the limits of the normal secretions of NH_3. This is noteworthy, because the patient was excreting a considerable amount of organic acid, and it is a well-established fact that NH_3 is the principal base to which the organic acids are united when they are excreted. It is clear that in this instance the organic acid must have been united to some other base than NH_3, and there is reason to think that the base is chiefly potassium.*

* This observation is not entirely conclusive as to whether the base removed by the organic acid were chiefly K or Na, for in our method of balancing the acids and bases of the urine these bases are not determined directly. In this method we assume that the Na of the urine corresponds closely to the Cl excreted, and the K is obtained by the difference, on the basis of this assumption. The results must, therefore, be regarded as only approximating the truth.

The excretion of the NH_3, the Na, and the K, during and before and after the period of restricted diet is indicated in the following table:

EXCRETION OF NH_3, Na, AND K IN CASE IX (24-hour periods).

Date.	Diet.	Excret'n of organic acid in terms of B-oxybutyric acid	Excretion of NH_3.		Excret'n of Na_2O in terms of Na.	Excret'n of K_2O in terms of Na.	Excretion of sugar.	
			Total.	Per ct.			Total.	Per ct.
March 18, 1901.	Carbohydrates moderately restricted.	9.26 gm.	0.82 gm.	2.42	6.69 gm.	5.10 gm.	174 gm.	4.7
March 26, 1901.	Carbohydrates excluded during 4 days.	1 "	1.08 "	3.27	7.08 "	3.32 "	65.45 "	2.75
April 1, 1901.	Carbohydrates moderately restricted.	10.07 "	1.31 "	4.14	4.98 "	4.82 "	101.2 "	3.68

The urine on which the first observation was made shows the excretion of K_2O in terms of Na to be nearly as great as the excretion of Na_2O in terms of Na. These are not normal conditions, since when a normal individual is eating plentifully, as in this instance, the Na_2O is only about one-half as abundant as the K_2O. In the second observation the K_2O has fallen to less than one-half the Na_2O, with very little change in the total Na_2O. This fall in K_2O corresponds to the period of strict diet and small excretion of organic acids, that is to the period in which there is no unusual demand from bases to neutralize acid. In the third observation the organic acids have again increased to considerable proportions, and the K_3O equals the Na_2O. We are led to the conclusion that it is chiefly the K which is concerned with the removal of the organic acid. If we had depended in this case on the study of the excretion of NH_3 to determine whether there was any pathologic excretion of organic acids we would have reached the conclusion that such acids were not being excreted. Probably the true condition could only have been shown by balancing the acids and bases as was here done, since diacetic acid was not detected and the yield of crotonic acid was very small and in one instance even questionable.

The patient to whom reference has just been made is slowly losing

weight, but is still a well-nourished and vigorous individual capable of doing exacting physical labor. The fact that the exclusion of carbohydrates no longer suffices to stop the glycosuria indicates a loss of assimilative capacity as compared with the conditions one year ago. The clinical indications are that this patient is likely to do well for many months in spite of a considerable excretion of organic acids at times.

Case X.

The next case in this category is that of a middle-aged man who came under the observation of Dr. E. K. Dunham. He first noticed the excessive amount of his urine about April 7, 1900. Between April 1 and May 1, 1900, that is, in one month, he had lost 50 pounds, but still weighed 147 pounds. He suffered from great thirst, anorexia, and debility, but was able to bring a large jug of his urine from Englewood, N. J., to the Carnegie Laboratory, carrying it part of the way. The urine for twenty-one hours amounted to 11,500 c.c., contained organic acids equal to 30.02 gm. of β-oxybutyric acid in twenty-four hours. The N of NH_3 equalled 17.55 per cent., and the total N of NH_3 was 3.32 gm. The ferric chloride reaction for diacetic acid was strong. In the twenty-four hours urine and sugar reached the enormous amount of 556.3 gm. The amount of oxybutyric acid excreted makes it probable that this man was not far from a fatal termination in coma, and it is most unfortunate that the subsequent history of the patient is unknown.

Case XI.

A somewhat similar but less acute case came under the observation of Dr. G. A. Spalding at St. Luke's Hospital. A man, aged twenty-eight years, lost 93 pounds in three months, and for six weeks previous to the analysis passed large amounts of urine. At the time of the examination the chief complaints were debility and great thirst. The urine for a portion of the twenty-four hours contained 6.01 gm. of oxybutyric acid. The quantity for twenty-four hours was probably two or three times this amount, judging from the N excretion. The N of NH_3 reached 9.70 per cent. Crotonic acid was easily obtained from the urine. The patient continued to lose weight and strength, but the ultimate outcome is not known.

Case XII.

The last observation to be included in this category relates to a male patient of Dr. C. C. Ransom, seventy-five years of age, who has had persistent glycosuria for several years. The general health is good, and the patient is said to be without symptoms. On November 4th the urine contained an amount of acid equal to 6.9 gm. of oxybutyric acid, with 7.08 per cent. of N of NH_3 and 0.98 gm. of NH_3. The urine contained 1.17 per cent. of sugar, there being 22.81 gm. in twenty-four hours. The patient has been in excellent health since this observation was made, and has been on a diet moderately restricted in carbohydrates.

On February 19, 1901, the urine contained 0.32 per cent. of sugar and only 2.2 gm. of oxybutyric acid, with 3.31 per cent. of N of NH_3.

Perhaps the most important fact brought out by the cases in this group is that a diabetic (Case VIII.) may live many months after the appearance of a very high percentage of N of NH_3 in the urine. Sandmeyer's reports on the cases studied and published together with Külz show some remarkable illustrations of this fact.[7] One patient (Case 414) died eleven months after the urine contained 3.740 gm. of NH_3 (average of three different urines); another (Case 415) lived fifteen months after the urine showed 7.230 gm. of NH_3, an enormous quantity. Treatment aside from restriction in diet seems to have had little to do with these remarkable instances of prolongation of life. In my Case VIII. the patient showed no improvement in symptoms when the alkali treatment was instituted.

CASES OF DIABETES IN WHICH THERE IS EITHER NO PATHOLOGIC EXCRETION OF ORGANIC ACIDS OR IN WHICH THE EXCRETION IS SMALL.

Date.	Clinical notes.	Acid in terms of	NH_3.		Glucose.		No. of case.
			N of NH_3.	Total NH_3.	Total.	Per ct.	
		Gm.	Per ct.	Gm.	Gm.	Per ct.	
May 8, 1900.	Female, aged 35 years; glycosuria six years; loss of weight, thirst, nervousness, cardiac weakness.	1.85	4.98	1.294	199.6	2.9	XIII.
Dec. 5, 1900.	Same patient; has continued to lose weight and strength.	None.	4.24	0.539	125	4.1	
Oct. 5, 1900.	Woman, aged 50 years, alcoholic neuritis; duration of glycosuria unknown; alcoholic delirium. Died suddenly November, 1900. No coma; interacinar pancreatitis.	1.85	6.29	0.58	34.23	3.4	XIV.
Nov.12, 1900.	Woman, aged 75 years; glycosuria six years; 3–4 per cent. sugar on repeated examination; moderate loss of weight, debility, slight somnolence.	1.62	4.08	.....	.....	(Aver.) 3.4	XV.
Nov.22, 1900.	Man, aged 30 years; strong, well nourished; glycosuria for two years. Was cured at Bellevue Hospital two years ago. Drinking hard for 2–5 weeks.	None.	5.52	0.12	208	4.16	XVI.
Feb.23, 1901.	Male, aged 54 years; glycosuria 10 years; from 1–4 per cent. glucose; formerly controlled by exclusion of carbohydrates; loss of 10 lbs. in three weeks owing to restricted diet; now gaining.	7.05	3.70	1.43	.....	0.39	XVII.
Mar. 7, 1901.	Same patient; carbohydrates excluded from diet for five days previous.	1.08	3.0	1.0	.....	0.06	
Mar.28, 1901.	Same patient on moderately restricted diet, gaining in weight and strength.	1.13	4.14	1.3	.....	0.88	
Feb.24, 1901.	Male, aged 61 years; glycosuria four years, 1–2 per cent.; disappears when carbohydrates are stopped. General health excellent; inclination to corpulency, no loss in weight; carbohydrates restricted.	1.4	4.42	0.81	46.48	2.8	XVIII.
Apr. 6, 1901.	Same patient on a diet only moderately restricted in carbohydrates. General condition is excellent.	3.36 no crotonic acid.	4.98	0.91	22.62	1.66	
Apr. 6, 1901.	Female, aged 60 years; glycosuria for several years; diet only slightly restricted as regards carbohydrates; no symptoms; well nourished.	3.2	4.75	0.69	.....	0.1	XIX.

The cases which fall into this group are, with two exceptions (Cases XII. and XIV.), examples of diabetes of mild form—that is, the patients have none of the obtrusive clinical evidences of diabetes, such as thirst, polyuria, and loss of weight and strength. In Case XIV. an alcoholic neuritis complicated the condition, and the sudden death was probably connected with the extensive myocardial changes. In Cases XVI., XVII., XVIII., and XIX. the prospects for life appear to be good. Case XIII. is one in which the patient is constantly losing weight and is doing badly in other respects. The excretion of organic acids is so small that the unfavorable symptoms cannot be brought into relation with them. Case XV. has also progressed unfavorably, with an inclination to somnolence, in spite of the small excretion of acids. In Case XVIII. the patient excreted 8.36 gm. of acid in terms of oxybutyric acid, but crotonic acid was not positively detected.

We cannot, however, feel certain that the urine contained no oxybutyric acid because of the imperfections in the methods of obtaining crotonic acid from urine. This case might perhaps have been included in the second group.

The Relation between the Excretion of Organic Acids and the Excretion of Glucose.

An examination of the figures relating to the excretion of acids and of sugar makes it quickly evident that the fluctuations in these constituents of the urine are by no means proportional. Thus in Case VIII. we find the following conditions:

	Sugar.		Acids.
	Per cent.	Total.	Gm.
October 13, 1900	3.57	110.7	13.15
November 20, 1900	4.54	147.6	0.98

Here we see a marked increase in the sugar excreted, with a very striking fall in the quantity of acid.

In Case IX. we find somewhat different conditions, as shown in the table (page 603). In this instance there was a considerable fall in the sugar, but the percentage of decrease in the acids is considerably greater.

Again, in Case XVII., although there was a fall nearly proportional in sugar and in acids, from February 23d to March 7th, this was followed on March 28th by a rise in the excretion of sugar, while the acids remained little changed. It is worthy of note that in each of these three instances the considerable fall in the excretion of acids followed a restriction in carbohydrates of the food. This fact appears to me to be of considerable practical interest. If a patient who is eating carbohydrates liberally has a considerable quantity of organic acids in the urine there is the chance and even the probability that a restriction in diet will be followed by a considerable fall in this excretion of acid. If, however, a patient passes the same quantity of acid as in the case just mentioned, in spite of the fact that he is getting no carbohydrates, the outlook is likely to be worse than in the former case; in other words, we must test the effect of diet upon the acids just as we test its effect upon the excretion of sugar. Other conditions remaining the same, a quick fall in the acids in response to diet is to be considered a favorable indication, while the persistence of a considerable excretion of acid, in spite of diet, is to be considered unfavorable.

It sometimes happens that considerable sugar is excreted where there is little excretion of acid. Thus in Case VII. we find on one occasion an excretion of 70 gm. of sugar with less than 0.4 gm. of acid, and on another occasion 81.17 gm. of sugar with 1.8 gm. of acid. On the other hand, in Case XIX. we find only 22.62 gm. of sugar with 8.36 gm. of acid.

Notwithstanding these discrepancies, it is true that large amounts of organic acids generally accompany large amounts of sugar, and, conversely, that a large excretion of sugar (more than 200 gms. per day) is usually associated with a considerable excretion of organic acids. A small excretion of sugar (25 gm.) is rarely accompanied with considerable amounts of organic acids; but, on the other hand, small quantities of acid often go with considerable amounts of sugar (75 to 200 gm. per day). (See Cases XIII. and XVI.)

A striking example of the independence of the sugar excretion and the acid excretion has already been referred to in connection with Case VI. Here the excretion of acids, as indicated by the N of NH_3, was very large at the time when the sugar almost disappeared from the urine.

The Nature of the Organic Acids in the Urine and Blood of Diabetes.

Since the independent and nearly simultaneous discovery by Minkowski and Külz of β-oxybutyric acid in the urine of diabetics many observations have been made which leave no doubt that when the NH_3 content of the undecomposed urine of diabetes is markedly increased the presence of β-oxybutyric acid can always be demonstrated. There are two properties of this acid which can be utilized for its detection. One is the formation of crotonic acid under the action of strong sulphuric acid and heat. The other is the levorotatory action of the acid.* By the use of methods based on these properties it has been possible to show that most of the organic acid in the urine of patients in coma or in the precomatose state is β-oxybutyric acid. Although diacetic acid is probably never absent under these conditions, there is reason to think that it is never present in the large amounts in which oxybutyric acid occurs. Of other acids in the urine in diabetes we know little. It seems by no means improbable that other organic acids are sometimes associated with β-oxybutyric and diacetic acid.

As yet there have been few observations on the blood and tissues of diabetics which throw light on the nature of the acid in the blood. It is natural to suppose that as the urine contains so much β-oxybutyric acid in diabetes, the blood must also contain it. The acid has indeed been discovered in the blood by such careful observers as Minkowski and Magnus-Levy. The quantity reported by Minkowski is more than 2.2 parts pro mille. Magnus-Levy found the acid in the liver, spleen, muscles, brain, and gastric contents. It is of interest that considerable acid was found in the brain. I was unable to obtain crotonic acid either from the liver, blood, or brain of a patient who died in diabetic coma, but do not consider that the presence of β-oxybutyric acid can be excluded in this case.

The discussion of the origin of the organic acids formed in diabetes and their relation to diabetic coma I shall reserve for another publication.

I desire to express my indebtedness to Dr. A. J. Wakeman for most of the analyses on which this paper is founded.

* The β-oxybutyric acid can also be extracted directly from the urine.

CONCLUSIONS.

It seems desirable to emphasize the following conclusions:

1. A careful balancing of the normal acids and bases of the urine makes it possible not merely to detect the presence of organic acids in the urine, but also to determine approximately the amount of such acids. The method recently described by Herter and Wakeman can be recommended as securing a greater degree of accuracy for the amount of labor involved than any other procedure.

2. The determination of the N of NH_3 is a useful procedure for clinical purposes, since it is probably true that a considerable excretion of organic acid (say 15 gm. oxybutyric or more in twenty-four hours) is always attended by an increased excretion of NH_3. As much organic acid as corresponds to 10 gm. oxybutyric acid may be excreted in twenty-four hours without causing an increased excretion of NH_3 (Case IX.). We cannot, therefore, rely on the ammonia output to detect moderate quantities of organic acid.

3. Where organic acids are removed in considerable amount without increasing the excretion of NH_3 the acid takes out other alkalies, probably in some instances chiefly K.

4. In cases of diabetic coma the urine always contains a large excess of organic acids and the N of NH_3 is usually increased to 18 to 25 per cent of the total N.

5. Crotonic acid can regularly be obtained from the urines of patients in diabetic coma.

6. The condition of diabetic coma is preceded by a period of days, weeks, or months, in which there is a large excretion of oxybutyric acid (20 gm. or more in twenty-four hours), and in which the N of NH_3 is largely increased.

7. Patients whose urines show or have shown a large excretion of organic acids are in danger of developing diabetic coma, but the N of NH_3 may temporarily rise as high as 16 per cent., and yet coma may be delayed for more than seven months (Case VII.). The persistent excretion of more than 25 gm. of β-oxybutyric acid indicates impending coma.

8. A patient passing 30 gm. of oxybutyric acid in twenty-four hours may still have enough energy and strength to be about all day and perform considerable muscular work (Case X.).

9. A patient who has been excreting very little organic acid and has gained weight may within a few months show the presence of considerable quantities of organic acid and die in typical diabetic coma (Case VII.).

10. When the urine contains little or no organic acid there is no immediate prospect of diabetic coma, but patients with such urine are probably liable to most of the other dangers that threaten diabetic patients. The relation between the degree of acid intoxication and the susceptibility to infection seems worthy of special experimental study.

11. Where the urine regularly contains more than 200 gm. of sugar per day there is usually considerable organic acid in the urine, and large amounts of acid, indicative of coma, are invariably accompanied by considerable or great glycosuria.

12. Sometimes there is much sugar and little or no acid in the urine, and sometimes there is considerable acid and little sugar. These facts render it desirable to examine the urine of diabetic patients at least once a month with reference to the amount of acid excreted, for the element of acid intoxication must be clearly separated from the element of glycosuria in our study of the progress of a case. In other words, we must recognize the acid intoxication as an important and sometimes as a dominant factor in the prognosis, and this element should be regarded even in those cases of diabetes which have the clinical indications of a mild type of the disease. We may thus hope to prolong life in many instances by taking precautions as to diet and out-of-door life which might not otherwise be deemed necessary.

13. The withdrawal of carbohydrate food frequently leads to a considerable reduction in the quantity of organic acids excreted. The reason for this is not yet clear, and the phenomenon deserves careful study.

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METABOLISM IN DIABETIC COMA, WITH ESPECIAL REFERENCE TO ACID INTOXICATION.

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THE present case of diabetic coma is reported (1) because of the extreme grade of the acidosis; (2) because diacetic acid was absent for several months before death; (3) because of various facts which developed in the examination of the urine, stools, vomitus, and contents of the gastrointestinal tract. These relate chiefly to the absorption of sodium bicarbonate, the estimation of urea in diabetes, the increasing percentage of ammonia to the total nitrogen excreted, the unusual amount of acetone as compared with β-oxybutyric acid, the diminution of the chlorin in the urine and its presence in the feces, and the excessive excretion of potassium.

History of the Case. A. W., a boy, aged fifteen years, became thirsty and tired in August, 1897. Since birth he had shown an infantile paralysis, most marked in the left foot, but his mind had always been active and his health good. His parents were well, and no case of diabetes had ever been known in the family. In August, 1898, he consulted Dr. James J. Putnam, who kindly transferred the case to me. At that time the patient's weight had fallen from 50.5 kilograms to 41.6 kilograms, and he presented the symptoms of a severe diabetic. Physical examination revealed little aside from the remains of the infantile paralysis. The breath did not give an acetone odor. The urine amounted to eight liters on August 18, 1898, and contained 520 grams of sugar, but no diacetic acid or acetone. Following the restriction of diet, the amount of urine on August 22d was two liters, and it contained 76 grams of sugar. Gerhardt's reaction for diacetic acid was marked. This reaction persisted until June 26, 1900, when it disappeared. It was absent July 31st and September 10th, but was found when the urine was next examined, October 14, 1900, the day which preceded the onset of coma. The diet of the patient during the greater part of these two years contained, in addition to the usual "strict diabetic diet," 500 c.c. of cream, two oranges, 15

grams of bread and a little whiskey. This diet was quite faithfully followed until the summer of 1900. At this time the patient clandestinely ate rather freely of carbohydrates. The condition of the patient was remarkable considering the severity of his illness. Two weeks before his death he spent the whole of two consecutive days at a country fair. The gain in weight amounted to nine kilos, and two days before his fatal illness was but one kilo below his best weight. The administration of sodium bicarbonate was begun August 22, 1898, and 10 to 20 grams were given daily without intermission for the remainder of his life. The sodium bicarbonate was not omitted even during the last four months, when the tests for diacetic acid were negative. For details regarding the course of the disease the reader is referred to Table I.

TABLE I.—PROGRESS OF DIABETES IN A BOY.

Onset, August, 1897.
Treatment began August 18, 1898. Weight, August 22, 1898, 41.6 kilos.
Death by coma, October 19, 1900. Weight, October 14, 1900, 49.5 kilos.

Date.	Amount.	Sp. gr.	Reaction.	Albumin.	Sugar.	Acetone.	Diacetic acid.	$NaHCO_3$	Weight.
1898									
Aug. 16	.....	1037	Acid	.....	+	.....	0	.....	
" 18	8000	1027	Sl. acid	0	520	0	0	10–20	
" 22	2000	1029	.....	.....	76	.....	+ +	"	41.6
" 24	3000	.....	.....	.....	...	.....		"	
" 29	4000	1033	.....	.....	268	.....	?	"	
Sept. 6	4000	1036	.....	.....	312	.....	0	"	45.5
" 12	2500	1034	.....	.....	...	.....	.....	"	44.8
" 15	4000	1032	.....	.....	...	.....	.....	"	44.9
" 19	4000	1033	Acid	0	228	.....	+	"	44.9
Oct. 1	5000	1038	.....	.....	415	.....	+ +	"	46.8
" 10	3000	.....	.....	.....	207	.....	+	"	
" 17	2500	1039	Acid	0	210	.....	+ +	"	
" 24	3000	.....	.....	.....	264	.....	+	"	46.8
" 31	3000	1040	Acid	Sl. trace	234	.....	+ + +	"	
Nov. 14	3500	1040	.....	.....	242	.....	.....	"	
" 21	3000	.....	Acid	0	171	.....	.....	"	
1899									
Mar. 13	3000	1043	.....	.....	246	.....	+ + +	"	49.1
Apr. 10	2500	.....	.....	.....	...	.....	+ +	"	48.4
May 15	2700	1045	.....	.....	213	.....	+ + +	"	48.6
June 21	4000	1040	.....	.....	...	.....	+	"	47.7
Aug. 11	.....	.....	.....	.....	...	.....	.....	"	48.4
Oct. 10	3000	1036	.....	.....	165	.....	+ + +	"	49.3
Dec. 4	3000	1031	.....	.....	...	.....	.....	"	49.2
1900									
Jan. 29	2750	1035	.....	.....	132	.....	+ + +	"	50.5
Mar. 20	3000	1034	.....	.....	147	.....	+ + +	"	50.6
Apr. 23	3000	1036	.....	.....	171	.....	+ +	"	47.3
June 26	3000	1034	.....	.....	231	Little	0	"	47.3
July 31	3500	1034	.....	.....	144	0	0	"	
Sept. 10	5000	1033	.....	.....	357	.....	0	"	47.8
Oct. 14	.....	.....	.....	.....	...	.....	.....	.....	49.5

The amount of urine is expressed in c.c. (cubic centimeters), the sugar and sodium bicarbonate in grams, the weight of the patient in kilos.

In the early morning hours of October 16, 1900, the patient was very restless and thirsty. This condition became aggravated during the forenoon, at which time the respiration changed and took on the characteristic type of

diabetic coma. At 4 P.M. he was conscious, but helpless. The pulse was 124 and the respiration 26. During the first sixteen hours of the day he had taken ten grams of sodium bicarbonate and some brandy. Sodium bicarbonate was now given in four-gram doses about every half hour, and 500 c.c. of a 3 per cent. solution of sodium bicarbonate was given by the rectum. For his thirst he took sodium bicarbonate in water and milk. The sodium bicarbonate given by the rectum was not retained. That given by the mouth, with one exception, was well borne. As the patient did not improve, but lost ground during the second half of the first day, 1000 c.c. of a 3 per cent. solution of sodium bicarbonate, dissolved in normal saline solution, was then injected intravenously. The effect was striking. The dyspnea and restlessness disappeared, the patient slept quietly for an hour, and passed the following day in comparative comfort.

During the first day he took in all 113 grams of sodium bicarbonate, on the second day 140 grams, but on the third day the sodium bicarbonate was not so well retained. The patient was not only somnolent but much weaker, and the dyspnea reasserted itself. This was temporarily checked by two intravenous injections of the sodium bicarbonate: one of 1500 c.c., the other 750 c.c. In all for this twenty-four hours he received not over 92 grams.

At the beginning of the fourth day the patient's condition was very poor. The temperature was 95.6°, and the pulse 132. He was within the pale of coma, and unable to keep down either food or alkali. Unconsciousness gradually came on, and he died three and one-half days after the onset of the complication.

Table II. presents a summary of the analyses of the urine and stools during the coma period.

The autopsy was performed by Dr. Oscar Richardson, of which the following is an abstract from his notes:

Body of a boy fairly developed, subcutaneous fat small in amount, skin and mucous membrane pale. Feet in the position of talipes equinus varus, more marked in the left foot. Tissues on section bleed very freely. Brain and meninges not remarkable. Vessels of meninges markedly injected. Sinuses free. The lungs, pleura, peritoneum, gall-bladder, bladder, prostate, stomach, and intestines presented nothing of note. The liver weighed 1826 grams, and on section was normal in appearance. The spleen weighed 165 grams, and on section was dark red in color and soft. The pancreas was rather small, dark red in color, and softer than usual. The kidneys weighed 195 and 196 grams. Capsules strip off, leaving a smooth surface. On section the tissue is firm, and the markings normal in appearance. The cortex averages 6 mm. Mesenteric glands were enlarged and grayish-red on section. Sections were hardened in Zenker's fluid and stained in methylene blue and eosin.

Liver: The lobular capillaries are dilated, and there is some atrophy of the liver cells in the central portion of the lobule. The liver cells throughout the section show a moderate amount of fatty metamorphosis.

Pancreas: The section presents nothing remarkable. The islands of Langerhans show no change.

Kidney: The section presents nothing remarkable.

Sections of the medulla and a small portion of the cord from the upper cervical region were hardened and stained after Pal's method.

Cord: Section from the upper cervical region shows in the anterior radicular zone of each side a small patch of degeneration of the nerve fibers. The anterior nerve root on one side, near the patch of degeneration and outside of the cord, shows degeneration of its fibers. Sections in the region of the decussation of the pyramids show degeneration in corresponding situations to those mentioned.

HISTORICAL RÉSUMÉ OF ACID INTOXICATION THEORY. The acid intoxication theory[1] of diabetic coma is of comparatively recent origin, but its development has been so uniform and logical that it has steadily added to the number of its adherents. Salkowski[2] found in 1873 that it was possible to withdraw alkalies from the bodies of rabbits by the administration of taurin, and that following such withdrawal death occurred. In the year 1877, Walter[3] observed a marked increase of the ammonia in the urine of a dog following the administration of dilute solutions of hydrochloric acid. Three years later Hallervorden[4] studied the excretion of ammonia in various diseases, and found that it was increased in diabetes. Instead of the normal amount of 1 gram, he found at times as much as 5.95 grams in twenty-four hours. As the urine was always acid in these cases, he explained the acidity by an excessive excretion of inorganic or possibly organic acids—products of carbohydrate metabolism. In 1883 Stadelmann[5] substantiated his work, but by a comparison of the mineral acids and bases, including ammonia, showed that the bases were greatly in excess of the mineral acids. This allowed but one conclusion, namely, that the acidity of the urine must be due not to inorganic but to organic acids. During the following year (1884)

[1] Those familiar with Magnus-Levy's work will see that in this account of the history of diabetic coma, as in many other particulars, I have drawn freely from his publications.

[2] Ueber die Möglichkeit der Alkalientziehung beim lebenden Thier. Virchow's Archiv, 1873, lviii. p. 1

[3] Untersuchungen über die Wirkung der Säuren auf den thierischen Organismus. Arch. f. exp. Pathol. u. Pharmakol, 1877, vii. p. 148.

[4] Ueber Ausscheidung von Ammoniak im Urin pathologischen Zustanden. Arch. f. exp. Pathol. u. Pharmakol., 1880, xii. p. 237.

[5] Ueber die Ursachen der pathologischen Ammoniak ausscheidung beim Diabetes Mellitus und des Coma diabeticum. Arch. f. exp. Pathol. u. Pharmakol., 1883, xvii. p. 419.

Minkowski[1] showed that this organic acid was β-oxybutyric acid, and that diacetic acid and acetone could easily be derived from it. Simultaneously E. Külz[2] made the same observation by discovering that the urines of severe diabetics after fermentation were levorotatory. But even before the identification of the acid Stadelmann recognized its importance in the pathology and treatment of diabetes, and especially diabetic coma. He saw the patient, in whose urine he found large quantities of acid die of diabetic coma. Furthermore, he was struck by the similarity between the coma symptoms and those of the rabbits in which Walter had produced an acid intoxication, and concluded that the cause was the same in each instance. Walter had found that when more than 0.9 gram of hydrochloric acid per kilo body-weight was injected into a rabbit death occurred in a few hours, with the symptoms of dyspnea, cardiac weakness, and collapse. But when he injected into these same rabbits, already poisoned with hydrochloric acid, solutions of sodium bicarbonate the above symptoms gradually passed off and the animals recovered. The acid intoxication theory received more or less recognition, especially by the Naunyn school, during the next few years, yet was not generally accepted.[3] In 1899, Magnus-Levy[4] strengthened the theory by the publication of more accurate methods for the isolation of the acid and by an account of a case of diabetic coma which was cured by the administration of enormous doses of sodium bicarbonate. In a second paper,[5] which has just appeared, he has added another case to the list of cures, bettered his former method for the estimation of the acid, and studied the excretion of β-oxybutyric acid in coma-free periods. This latter study has also been carried on by Herter, and will be reported in this same volume.

Discussion of the Period Before Coma. It has already been mentioned in connection with the case under discussion that diacetic acid was absent from the urine when the patient first came under

[1] Ueber das Vorkommen von Oxybuttersäure im Harn bei Diabetes Mellitus. Arch. f. exp. Pathol. u. Pharmakol, 1884, xviii. p. 35.

[2] Ueber eine neue linksdrehende Säure (Pseudo-oxybuttersäure). Zeitsch. f. Biol., 1884, xx. 165.

[3] Von Noorden. Die Zuckerkrankheit. Zweite Auflage. Berlin, 1898, p. 98. Berliner klin. Wochensch., 1900, No. 49, p. 1117.

[4] Die Oxy-buttersäure u. ihre Beziehungen zum Coma diabeticum. Arch. f. exp. Pathol. u. Pharmakol., 1899, xlii. p. 149.

[5] Untersuchungen über die Acidosis im Diabetes mellitus und die Säure-intoxication in Coma diabeticum. Arch. f. exp. Pathol. u. Pharmakol., 1901, xlv. p. 389.

observation. Following the change in diet, it appeared and persisted until July 26, 1900, not to be found again until the day of coma. No examination of the urine took place between September 10, 1900, and October 14, 1900, the day on which coma began. Diacetic acid has been and remains one of the best danger signals of threatening coma, and its absence for months preceding coma is exceptional. Stadelmann[1] records a case of the absence of acetone and diacetic acid, but the amount of ammonia at about the same time was 12.2 grams, and the excess of bases four days later reached 6 grams. Hesse[2] and Germar[3] observed another patient whose urine immediately before the onset of coma gave no reaction with ferric chlorid. Recently von Noorden[4] has published an instance similar to mine in which the acid, though present for over two years in a patient treated by Naunyn and himself, at length disappeared for several weeks. The amount of ammonia in twenty-four hours was about 1 gram in contrast to 6 to 8 grams, which had been found ten months before. At the time the diacetic acid was absent the patient observed no diabetic rules. Von Noorden's observation, as well as mine, was made in July, 1900. Both patients had had diacetic acid for two years, and more or less simultaneously with the giving up of a fairly strict diet ceased to show the Gerhardt reaction. But in each patient the acid later reappeared, and both died in October, 1900, of diabetic coma. Without an explanation of the appearance of the acidosis, its persistence for nearly two years, disappearance for the four months preceding coma, and reappearance during the same, the acid intoxication theory of Stadelmann would appear unreasonable. The solution may be that which has lately been most clearly enunciated by Naunyn.[5] I refer to the secondary oxidation of these acid bodies in the presence of carbohydrates—a theory which has long been considered probable.

The oxidation of acetone and diacetic acid requires the simultaneous oxidation of carbohydrates. The basis of this theory depends on the work about to be described.

[1] Loc. cit., pp. 428 and 432.
[2] Zur Behandlung des diabetischen Coma. Berl. klin. Wochen., 1888, p. 379.
[3] Loc. cit. Stadelmann. Klinisches und Experimentelles über Coma diabeticum u. seine Behandlung. Deut. med. Wochen., 1889, p. 938.
[4] Die Zuckerkrankheit und ihre Behandlung. dritte Auflage. Berlin, 1901, p. 110.
[5] Der Diabetes. Die Deutsch Klinik. Berlin, 1901, Bd. iii. p. 15.

By the researches of Jänicke[1] and Rosenfeld[2] it became evident that when carbohydrates were withdrawn from the diet of a healthy man acetone and diacetic acid appeared in the urine. Hirschfeld[3] some years later, by a series of observations on diabetic patients, found that it was not necessary to remove all the carbohydrates. The same result was produced if only the greater part were removed, and that in general the severer the case of diabetes the more carbohydrates could be taken, and yet the reaction for acetone and diacetic acid in the urine be obtained. Finally, Gerhardt and Schlesinger[4] demonstrated on themselves that not only acetone and diacetic acid, but β-oxybutyric acid also, appeared in the urine when the diet consisted exclusively of meat and fat. All of these observers agreed that when even a moderate amount of carbohydrates were taken acetone, diacetic acid, and β-oxybutyric acid soon disappeared from the urine. It was not necessary even that the carbohydrates be given as such in a healthy person, since Hirschfeld showed that when a large amount of proteid material was given the patient enough carbohydrate was formed in the body out of it to take the place of ordinary carbohydrate foods. Magnus-Levy[5] was able to show that B-oxybutyric acid in severe cases of diabetes disappeared when, under treatment, the tolerance of these patients for carbohydrates rose and the individuals assimilated the carbohydrates in their food.

The explanation of the present case would, therefore, be as follows:

At the beginning of treatment the patient was living on a diet rich in carbohydrates. A sufficient amount of these was oxidized to ensure the oxidation of his acetone, diacetic acid, and β-oxybutyric acid, and consequently no acetone or diacetic acid was found in the urine. The carbohydrates were in part withdrawn, and so little of the remaining amount allowed him was oxidized that diacetic acid appeared in the urine. Living as he did on a considerably restricted diet for the next two years, the acid constantly escaped oxidation, and

[1] Jänicke. Beitrage zur sog. Acetonurie bei Diabetes melitus. Deut. Archiv f. klin. Medicin. 1881, p. 108.

[2] Rosenfeld. Ueber die Entstehung des Acetons. Deut. med. Wochen., 1895, S. 683.

[3] Hirschfeld. Beobachtungen über die Acetonurie und das Coma diabeticum. Zeitsch. f. klinische Medicin, 1895, xxviii. p. 176, and 1896, xxxi. p. 212.

[4] Ueber die Kalk- und Magnesianausscheidung bien Diab. mel. u. ihre Beziehung der Ausscheidung abnormer Sauren. Arch. f. exp. Pathol. u. Pharmakol, 1899, xlii. p. 106.

[5] Loc. cit. Arch. f. exp. Pathol. u. Pharmakol., 1901, xlv. p. 403.

was excreted as such. At the end of this time, when he discarded a fairly strict diet and ate large amounts of carbohydrates, though the greater part of these was undoubtedly excreted, enough was oxidized to prevent the appearance of diacetic acid in the urine. The disease progressed, and the time came, gradually or suddenly, I do not know which, when little carbohydrates, either taken as such in the food or formed from proteids in the body, attained oxidation, and as a consequence the acidosis not only appeared, but appeared in strength sufficient to cause coma. The same explanation might apply to von Noorden's case already mentioned.

For most cases of diabetes this explanation will certainly hold. But it will not account for the marked acidosis which was present in Stadelmann's case, or for Hesse's patient, whose urine on the day of coma gave no ferric chlorid reaction. A case which has recently occurred in Dr. Pfaff's practice also appears to be governed by other considerations. The patient is a middle-aged woman, who has a diabetes of moderate severity. For several months there has been diacetic acid in the urine. Of late the sugar has not only disappeared, but the patient has acquired a tolerance for carbohydrates and takes a few ounces daily. But the diacetic acid still persists in the urine. The organism retains its power of oxidizing carbohydrates in small amounts, yet the secondary oxidization of diacetic acid is interfered with. I do not remember to have seen the report of a similar case.

METABOLISM IN COMA. The urine and stools were accurately saved from about six hours after symptoms of coma appeared until the patient's death, three days later. (See Tables II. and III.) The amount of urine was greatest on the second day, and the acids excreted reached their maximum on this day also. Indeed, the amount of acids varied directly with the amount of urine. Magnus-Levy[1] noted this relation in both of his cases which recovered. Diuresis favors the excretion of these acids, and as β-oxybutyric acid is only excreted in dilute solution this may be the explanation of the occasional recovery of patients from diabetic coma by the use of diuretics and normal salt infusions. On October 16th to 17th the percentage of β-oxybutyric acid in the urine was 0.924, on October 17th to 18th it was 0.993, and on October 18th to 19th it was 0.919. In all

[1] Loc. cit.

TABLE II.—METABOLISM IN DIABETIC COMA.

Date.	Am't.	Sp.gr.	Reaction.	Albumin.	Sugar. Polarization.	Sugar. Fehling's.	Sugar. Total amount	NH_3	Nitrogen.	Ratio $N(H_3)$ to N	Extracted. Acetone.	Extracted. Diacetic reckoned from acetone	Extracted. B-oxybutyric.	Calculated B-oxybutric Diacetic acids from Extraction.	Calculated B-oxybutric Diacetic acids from Excess bases.	$NaHCO_3$ administered.	
Oct. 15-16	4000 ±	1036	Acid	Sl. trace	6.2	6.9	276 ±	1.99 ±	.....	.....	.....	.....	.....	.....	.....	.....	Coma began during last 6 hrs.
" 16-17	6050	1024	"	Trace	1.8	2.6	167	3.03	18.5	1 : 7.4	17.1	30.1	55.9	86.0	108.1	113	Coma relief. 24 h. after onset.
" 17-18	9700	1023	"	Sl. trace	1.2	2.4	233	8.07	23.8	1 : 9.4	32.3	56.8	96.8	153.1	180.7	140	Coma relieved.
" 18-19	7600	1019	"	Sl. trace	0.5	0.8	61	4.39	18.7	1 : 5.1	26.7	47.0	69.8	116.8	148.6	92	Coma returns; temp. relief.
" 19	800	1018	"	Trace	0.5	1.2	10	0.63	2.1	1 : 4	.....	.....	.....	.....	.....	6	Coma deepens; death.
Autopsy	455	1018	"	L. trace	1.0	1.3	6	0.41									

TABLE III.—EXCRETION OF BASES AND ACIDS DURING DIABETIC COMA.

Date.	Bases. NH_3	Bases. Na	Bases. K	Bases. CaO	Bases. MgO	Acids. P_2O_5	Acids. Cl	Acids. SO_3	Ur.	Sum of equivalents. Bases.	Sum of equivalents. Acids.	Excess of basic equivalents.	Calculated amount of B-oxybutyric diacetic acids.	Na in $NaHCO_3$ administered.
Oct. 16-17	3.03	20.23	5.21	0.97	0.18	3.17	1.69	2.91	>1	27.4	4.45	23.95	108.1	31.0
Oct. 17-18	3.06	33.80	8.87	0.49	0.19	3.40	1.06	2.23	>1	43.78	3.76	40.02	180.7	38.4
Oct. 18-19	4.39	26.10	6.47	0.57	0.18	3.78	1.15	1.59	>1	36.53	3.63	32.90	148.6	25.2

Magnus-Levy's[1] cases he has never met with over 0.6 per cent. of β-oxybutyric acid outside of coma, and only exceptionally in coma, with as much as 1.5 per cent. This relation between the amount of urine and the amount of acid excreted is an immensely practical one and one of the cardinal factors in the successful treatment of coma.

Albumin was present, but never exceeded a large trace.

Casts were looked for in the centrifugalized urine on each day, but were not present even in small numbers, except in the urine found in the bladder. This accords with Naunyn's[2] experience, but is in marked contrast to that of Aldehoff,[3] who has never failed to find casts, as described by E. Külz, in typical diabetic coma. In the urine found in the bladder they were very abundant. This, Professor Wood, of the Harvard Medical School, tells me, is a common occurrence in diseases other than diabetes, and is not of significance

The amount of sugar in the urine on the day preceding coma was about 276 grams; on the first day of coma it was 167 grams; on the second day 233 grams, and on the third 61 grams. This is quite according to rule, and is readily explained. During coma so little food is taken that the patient is in a state of under-nutrition, which of itself will lead to a reduction of the sugar output. For this reason the amount of sugar in the urine varies at such a time inversely with the general well-being of the patient. Leaving out the estimation of the day preceding coma, because that result was only approximate, we see that on that day, during which the patient was in best condition, the amount of sugar was the greatest; on the day upon which the coma was coming on it was less; but on the last day of coma it was least of all. The reaction of the urine was acid throughout. This is significant because it is a ready measure of the acidosis. No simple procedure gives so definite an idea of the amount of acid excreted by a severe diabetic as the attempt to neutralize the urine by the administration of sodium bicarbonate. A neutral or alkaline reaction is obtained, as a rule, in the urine of a healthy individual when 10 to 15 grams of sodium bicarbonate are given. To produce this same result in a diabetic patient of the severe type, it is not so very uncommon to require 50 grams. Often before the end is attained the sodium bicarbonate must be given for several days.

[1] Loc. cit., Bd. xlii. p. 199.
[2] Loc. cit., p. 298.
[3] Külz. Klinische Erfahrungen über Diabetes Mellitus. Jena, 1899, p. 459.

Next to the sodium bicarbonate as a ready measure of the acidosis comes the determination of the ammonia. The normal individual excretes about 1 gram of ammonia per day to 15 grams of nitrogen —that is, about 7 per cent. of the nitrogen in the urine is in the form of ammonia. As has been mentioned above, Hallervoden[1] discovered that this relation was much changed in diabetes, instead of 7 per cent. 20 per cent. being not uncommon. The highest percentage of nitrogen, in the form of ammonia to the total nitrogen, which I have found reported is in Magnus-Levy's second case,[2] in which it reached 30 per cent.[3] When sodium bicarbonate is given to a severe diabetic the amount of ammonia in the urine decreases,[4, 5] because the sodium obviates the necessity of synthetic production of an alkali in the body. Case IV. of Magnus-Levy's series[6] shows well how the amount of ammonia falls when alkalies are used. On the first day no sodium bicarbonate was given, and the percentage of nitrogen in the ammonia to the total nitrogen was 18 per cent. On the second and third days 72 grams of sodium bicarbonate were given, and the percentage fell on the second day to 13 per cent., and on the third day to 12 per cent. At the same time this makes it obvious that when sodium bicarbonate is administered the ammonia in the urine is no longer a safe guide for the acidosis. An increase in the ammonia, should it occur at such a time, would be of marked significance and a sign of very unfavorable omen. Such a change, in fact, takes place in our case. On the first day of coma, though 113 grams of sodium bicarbonate were given the patient, the ratio between the nitrogen in the ammonia and the total nitrogen was more than twice the normal and was one to seven. On the second day, when it is remembered the patient had come out of coma, the proportion fell to one to nine. This, however, was after the administration of even more sodium bicarbonate, 140 grams. As the coma returned on the third day, new efforts were made by nature to check the advancing acidosis, and the ratio rose to the highest yet—one to five. It is interesting to note that in the last eight hours of the patient's life the ratio was still higher, namely, one to four. The highest

[1] Loc. cit.

[2] Loc. cit., Bd. xlv. p. 401.

[3] Unfortunately, the amount of nitrogen is not given in Stadelmann's case, whose urine contained 12.2 grams of ammonia in twenty-four hours.

[4] Minkowski. Loc. cit.

[5] Stadelmann. Ueber die Behandlung gewisser Formen von. Diab. mellitus mit Alkalien. Arch. f. klin. Med., 1886, Bd. xxxviii. p. 302.

[6] Loc. cit., Bd. xlii. p. 181.

total amount of ammonia for any one day was 4.39 grams. Stadelmann[1] records 12.2 grams, but this was at a time when the alkaline therapy was not employed.

Why is it that in these severe cases the amount of ammonia falls when sodium bicarbonate is given, even though the acidosis is not overcome? Why does not the body continue to protect itself with the production of large amounts of ammonia? Why when sodium bicarbonate is not given does not still more nitrogen leave the body in the form of ammonia instead of urea? Finally, why is it that when the acidosis is combated by the administration of large doses of sodium bicarbonate and the urine is alkaline that the ammonia does not wholly disappear? At present these questions cannot be satisfactorily answered, and speculation is unprofitable.

TABLE IV.—EXCRETION OF NITROGEN, AMMONIA, AND UREA DURING TWO DAYS OF DIABETIC COMA.

Date.	N	NH_3	Urea.	
			Braunstein's.	Squibb's.
October 18	23.8	3.07	43.6	80
" 19	18.7	4.39	29.6	48

In this connection your attention is called to Table IV., which shows the amount of urea passed on the last two days of coma as estimated by Squibb's[2] and Braunstein's[3] methods. The molecular weight of nitrogen in urea constitutes nearly one-half the weight of the molecule. It is thus readily seen that when the patient excreted 23 grams of nitrogen on October 18th it was impossible for the urine on that day to have contained more than twice that amount of urea, namely, 46 grams. By Squibb's apparatus, however, I obtained 80 grams of urea. On October 19th the relation was somewhat similar. This led me to investigate the matter, and I found that acetone, β-oxybutyric acid, or ammonia alone, when introduced into the Squibb's apparatus, acts like urea. To settle the point, the amount of urea on these two days was analyzed by Braunstein's

[1] Loc. cit., Bd. xvii. p. 428.
[2] Ogden. Examination of the Urine. Philadelphia, 1900.
[3] Braunstein. Hoppe-Seyler's Zeitsch. f. Phys. Chemie, 1900, xxxi.

method. Three analyses were made in each case. By this method the amount of urea was obtained which was consistent with the other facts in the case. Squibb's method for the estimation of urea is not of value in a severe case of diabetes. One of my assistants hopes to show, however, that it still has uses in the practical treatment of diabetes. Stadelmann[1] mentions a case in which the excretion of urea reached 134.9 grams. It has not been possible for me to test the accuracy of the method which he employed. In looking over my records I find in the first case of diabetes which ever came under my observation that on August 31, 1893, the amount of urea as determined by Squibb's apparatus was 106 grams. The total quantity of urine on this day was 3000 c.c., and it is striking to note that on this day the quantity of urine was less than at any time between August 4, 1893, and January 31, 1894, and also that the amount of sugar excreted on the same day was the smallest in amount during the same period. When the patient on a free diet excreted 10,000 c.c. of urine, the urea was but 44 grams. There is little doubt that the high amount of urea on August 31st was really simply a combination of urea, acetone, ammonia, and β-oxybutyric and, perhaps, other acids, the great increase of these latter bodies having been brought about by restrictions in diet.

Increased proteid metabolism was long ago considered to be an accompaniment of coma. Recently, Sternberg[2] has advocated the same view. Weintraud,[3] Magnus-Levy[4] and others have shown this not to be the case. The weight of my patient is a striking confirmation of their views. Two days before the onset of coma it was within one kilo of the highest it ever attained preceding or during his illness. The amount of nitrogen also is against any excessive nitrogenous metabolism and Sternberg's amidobutyric acid theory. On the 16th to 17th the nitrogen was 18.5 grams; on the 18th to 19th, 18.7 grams. On these two days he ate little. On the intermediate day, when he ate freely and took large amounts of liquid, the nitrogen rose to 23.8 grams, which is not inconsistent with his diet and the

[1] Arch. f. exp. Pathol. u. Pharmakol., 1883, xvii. p. 434.

[2] Chemisches u. Experimentelles zur Lehre von Coma diabeticum. Zeitsch. f. klin. Med., 1899, xxxviii. p. 74.

[3] Ueber die Ausscheidung von Aceton, Di-Acetsäure, u. B-oxybuttersäure beim Diab. Mel. Arch. f. exp. Pathol. u. Pharmakol., 1894, xxxiv. p. 169.

[4] Loc. cit., Bd. xlii.-xlv.

marked diuresis. It is a well-known fact that diabetic coma comes on unexpectedly when patients appear to be in fair health. It is not so thoroughly appreciated that it may develop even when their nutrition is at its best. This I have seen in several cases.

ACETONE. This was estimated by the Messinger-Hüppert method. Control tests were made with normal and other diabetic urines and with urine to which chloroform (the preserving agent employed) had been added. The amount of acetone obtained is unusually high. Magnus-Levy[1] says that 10 grams have been found only once or twice in adults. In his patient during coma the amount of acetone—and, of course, this includes diacetic acid—reached 15, 16, and 18.7 grams. On the first day of coma my patient excreted 17.1 grams, on the second 32.3 grams, on the third 26.7 grams—a larger amount than I have been able to find elsewhere recorded. It is unfortunate that we are not able to say how much existed preformed as acetone and how much as diacetic acid, but from von Arnold's[2] work it is probable that it is mostly as diacetic acid. Weintraud[3] and Mayer[4] both showed that acetone was increased when sodium bicarbonate was given. This was obvious in both of Magnus-Levy's cured cases as well as in mine. Magnus-Levy explains this as not due to any oxidizing action of the alkalies when introduced into the body, but rather to the fact that the sodium bicarbonate favored the excretion of the acid by forming a salt. Why the quantity of acetone in my case should be so high relatively to the quantity of β-oxybutyric acid as compared with other cases of coma may or may not be important. The presence of acetone in large amount shows how extensive the deranged metabolism is, but it also implies that a great deal of β-oxybutyric acid is being produced, of which a considerable part is carried to the acetone stage. Weintraud[5] saw diacetic acid increase when sodium bicarbonate was given, but not the β-oxybutyric. This occurred in light cases. The inference might be drawn that my case was not so severe a type as those of Magnus-Levy, since in my case the β-oxybutyric acid was more thoroughly oxidized. To be sure, his patients lived and mine died, but his cases were in younger persons—thirteen and twelve years

[1] Loc. cit., Bd. xlii. p. 184.
[2] Ueber. Nachweis u. Vorksommen der Acetessigsäure in pathologischen Harnen. Cent. f. inn. Med., 1900, p. 417.
[3] Loc. cit., p. 183.
[4] Loc. cit., p. 178, Weintraud's article.
[5] Loc. cit.

of age respectively. He calls attention to the fact that cures in diabetic coma have almost invariably taken place in children.

The acetone odor to the breath was not particularly striking in this patient, and I have observed the same circumstance in another case of coma where the patient for weeks preceding had taken large doses of sodium bicarbonate. It would be interesting to note whether in patients with diabetic coma who have not gone through the alkaline treatment the odor of acetone is more marked than in those who have taken alkalies. This is a clinical fact which confirms von Arnold's statement mentioned already—that little of the acetone exists preformed.

β-OXYBUTYRIC ACID. The β-oxybutyric acid was extracted by a method taught me by Magnus-Levy. This he has since published.[1] Briefly it is as follows: To 400 c.c. of urine are added 15 or 20 grams of ammonium sulphate, and the urine evaporated to about 80 c.c. An aliquot part of the filtrate corresponding to 250 c.c. of urine is mixed with a dilute solution of sulphuric acid saturated with ammonium sulphate. This acid fluid is shaken for fifteen minutes with 400 c.c. of ether. If 900 c.c. of ether are used, twelve extractions are sufficient. The ether after each extraction is washed with a small amount of water (25 c.c.), the same portion being used throughout. Finally, the combined ether extracts are distilled and the β-oxybutyric acid remains as a clear dark-brown liquid. In addition to β-oxybutyric acid, Magnus-Levy[2] has found that the residue contains hippuric acid, volatile fatty acids, and a remaining acid equivalent, which he was unable to identify and isolate.

In the present case 900 c.c. of ether were used for each extraction, of which ten were made with the urine passed on the 16th and 17th, and five for that of the other two days. In the two latter instances more acid was obtained by five extractions than by ten. The method consumes much time, and, unfortunately, is liable to unlooked-for errors. By this method on the first day the amount of oxybutyric acid thus isolated and determined by means of the polariscope, using the new rotary angle[3] of 24.1°, was 55.9 grams, on the second day 96.3, and on the third 69.8. If we add to this the diacetic acid excreted, estimating that the acetone obtained was simply derived from

[1] Loc. cit., xlv. p. 390.
[2] Loc. cit., xlv. p. 397.
[2] Loc. cit., xlv. p. 391.

diacetic acid, we have a total of diacetic and β-oxybutyric acids extracted for the two days of 86.0, 153.1, 116.8 grams, a larger amount than I have been able to find elsewhere reported.

The only other reliable method of determining the acidosis is by the estimation of all the acids and bases. This was employed by Stadelmann and referred to in the earlier part of this paper. Here, of course, we estimate not one acid but many. The chief acids are β-oxybutyric and diacetic. For a discussion of the other acids the reader is referred to Magnus-Levy's second article. The estimation of the total acidosis by a calculation of the β-oxybutyric acid equivalent for the excess of bases is more accurate than the methods of extraction. This is natural, not only because the quantitative estimation of inorganic elements is much simpler than a quantitative extraction of organic compounds, but also because of the various volatile acids which are present to a greater or less degree. The results obtained by extraction are always smaller than those obtained by calculation of the excess of bases. In my case the difference approximates closely to the difference obtained by Magnus-Levy in his cases. Thus on the first day the acidosis by extraction was 86 grams; by excess of bases, 108.1 grams; on the second day, 153.1 as contrasted with 180.7; on the third, 116.8 in contrast to 148.6.

During the three days of the coma 437 grams of acid were excreted. This amounted to three grams per kilo body-weight per day. Taken in conjunction with Magnus-Levy's two cases, this goes to show that the formation of large amounts of acids in diabetic coma is not simply a coincidence, as has recently been suggested by Sternberg.[1]

A comparison between the case just reported and those of Magnus-Levy which successfully recovered from coma shows that our patient, excreting 3 grams per kilo body-weight, died, while his, excreting respectively 4 and 4.5 grams per kilo body-weight, lived. The total amount of acids excreted, to be sure, was greater in the present case; but this is not so much to the point as the amount of acid in proportion to the weight of the individual. During the coma period 32 grams of sodium in the form of sodium bicarbonate were taken daily by our patient, but in Magnus-Levy's two cases 35 grams were given. But in our case and in his earlier case the loss of sodium in the

[1] Zeitsch. f. klinische Medicin, 1899, xxxviii. p. 69.

stools (see Table V.) was very great, while in his second case it was very slight. Sodium was also lost in my case in the vomitus, and a considerable amount also remained unabsorbed in the gastrointestinal contents (see Table VI.). The reaction of the urine remained acid to the end, and if more alkali had found its way into the circulation it is a legitimate inference that more acid would have been excreted. It is the amount of acid which remains in the body that kills the patient, for on the second day of the coma period in my case, the day during which 181 grams of acid were excreted, the patient, though in a very critical condition, was out of coma.

TABLE V.—ANALYSES OF FECES.

October 16–17	Na	7.3	grams in twenty-four hours.
" 17–18	K	2.13	" " " "
" 18–19	CaO	0.25	" " " "
	MgO	0.05	" " " "
	Cl	3.10	" " " "

TABLE VI.—ANALYSIS OF VOMITUS AND CONTENTS OF GASTRO-INTESTINAL TRACT.

Na	5.72	grams.
K	11.50	"
Cl	5.80	"

The formation and excretion of β-oxybutyric acid outside of coma has been studied by Magnus-Levy and Dr. Herter. Magnus-Levy found that, under the administration of large doses of sodium, the amount of β-oxybutyric acid excreted reached 60 grams, and yet the patient showed no signs of coma. As soon as this amount was exceeded, symptoms developed. It is questionable whether an individual would be able to endure an acidosis of the intensity which this amount implies were he not previously protected by the administration of large doses of sodium bicarbonate.

Comment has already been made in passing on the increasing ratio of the nitrogen in the ammonia to the total nitrogen as the final symptoms of coma came on. This was not the only effort which the body made to avert the threatened acid intoxication. This is obvious from a study of the calcium in the feces and urine. Normally 90 per cent. of the calcium in the body is excreted in the stools, but in this instance metabolism was altered and the calcium in the urine was in excess. During the coma period the stools contained 0.75 grams of calcium, but the urine 2.03 grams, or 63 per cent. This confirms Gerhardt's

and Schlesinger's[1] work, who found 59 per cent. of the total calcium in the urine of a severe diabetic, and 41 per cent. in the stools. When no alkalies were given the quantity in the stools fell to 23 per cent. Magnesium is normally excreted chiefly in the urine, 40 per cent. only appearing in the feces. In our case, however, during the three days there was 0.55 gram in the urine, but only 0.15 gram in the stools. The percentage of magnesium excreted in the urine was, therefore, 73 per cent. instead of the normal excretion of 60 per cent. Thus, again, nature neutralized the acids from her own resources.

The amount of sodium found in the urine during the three days was 80 grams. During the same time approximately 95 grams were given as sodium bicarbonate. Table V. shows, however, that 22 grams, or 23 per cent., were unabsorbed and lost in the stools, presumably on account of the diarrhea. Such an excessive loss is very unusual. Kozerski,[2] who studied this question, found in diarrhea that only about 15 per cent. escaped absorption. The contrast between the absorption of sodium in my case and the second case of Magnus-Levy's is remarkable, for in his but half of 1 per cent. was excreted in the feces. When we deduct also the sodium found in the vomitus and gastrointestinal contents (see Table VI.), 5.72 grams, we have only a total of 67 grams of sodium, equivalent to 244 grams of sodium bicarbonate absorbed during the three days. At the time of the patient's illness it was supposed that he was taking nearly double this amount. This is only another illustration of the erroneous conclusions to which bedside observations not based on scientific data may lead. Bearing this in mind, it is easier to understand the recovery of Magnus-Levy's cases and the fatal issue of mine. Some sodium was contained in the milk which the patient took during the three days, but the balance of the sodium must have come from that already stored up in the body. This supply, however, is incapable of neutralizing more than about 80 grams of β-oxybutyric acid.[3]

The quantity of potassium, as can be seen by consulting Tables IV. and V., was high in both urine and stools; in fact, I have met with no instance in which as much potassium was present in the urine as was

[1] Ueber die Kalk- und Magnesian ausscheidung beim Diabetes Mellitus und ihre Beziehung zur Ausscheidung abnormer Säuren. Arch. f. exp. Pathol. u. Pharmakol., 1899, xlii. p. 83.

[2] Loc. cit., by Magnus-Levy. Arch. f. exp. Pathol. u. Pharmakol., 1901, xlv. p. 407.

[3] Magnus-Levy. Arch. f. exp. Pathol. u. Pharmakol., 1899, xlii p. 194.

excreted by my patient on the second day, namely, 8.87 grams. Stadelmann and Magnus-Levy both found the same increase of potassium in their cases. This would also appear to be due to some deranged metabolism. Kozerski[1] has shown that such an increase takes place when large doses of sodium bicarbonate are given. In this case, however, less sodium bicarbonate was given than in some others, yet the amount of potassium is greater.

The chlorin was very low in my case in the urine, and amounted to 1.7 grams, 1.1 grams, and 1.2 grams on the three days respectively. It amounted to 9.3 grams in the stools, and in the vomitus and gastrointestinal contents 5.8 grams more were found. Taking the total amount, the excretion of chlorin is approximately normal. In Magnus-Levy's sixth case the chlorin was only 0.6 gram on the day the most acid was excreted. Stadelmann[2] observed this point, and showed that when there was diarrhea in these cases chlorin would be found in the stools, presumably having combined with the sodium in the stomach. Magnus-Levy records no diminution of chlorin in the urine in one case of diabetic coma, but in this case diarrhea was absent. This is quite in line with the explanation just given.

In diabetic coma we deal with an individual who is undergoing tremendous alterations in his metabolism. Substances which once served as nutrients are now no longer of avail, and the more the normal metabolism of these substances is interfered with the more the various products which quite likely are normally formed in the process of katabolism escape complete oxidation and appear in the urine. Of these substances we are at present acquainted with one group—β-oxybutyric acid and its derivatives. We know this is harmful to the body, not because of any specific quality which it possesses, but from the acid radical which it contains. *A priori*, we should consider the formation of 437 grams of an acid in the body enough to cause changes threatening to the life of an individual. But the body itself is the best witness to this fact, first, in its increased production of ammonia, and second, in the altered excretion of calcium and magnesium. We have a direct relation between the symptoms and the acidosis. On the second day of the coma period, the day during

[1] Loc. cit., by Magnus-Levy, Bd. xlii.

[2] Loc. cit., by Magnus-Levy, Bd. xlii.

which the patient was most free from coma, not only was the ratio of ammonia to the total nitrogen the least, but the acids removed from the body the greatest. When coma returned the ammonia-nitrogen ratio increased. At the present time the number of cases in which β-oxybutyric acid has been demonstrated during coma is well toward 100. The present case is distinguished by its severity, and thus lends weight in a more than usual degree to the already accumulated evidence that diabetic coma is the result of an acid intoxication.

In closing I wish to express my indebtedness to Professor Franz Pfaff for his interest and help in this investigation.

NOTE.—The inorganic analyses and the estimation of urea by Braunstein's method were performed for me by Mr. G. W. Knight. The methods for the inorganic analyses were the same as those employed by Magnus-Levy.

DISCUSSION.

DR. VAUGHAN: The subject presented in these papers is one of great interest, and I desire to speak some words of praise for the excellent work just reported here. There are one or two practical points which I desire to mention in this connection. I think that it must be admitted that we do not yet know the nature of a poisonous agent in what we call the acid intoxication of diabetes. It probably is not β-oxybutyric acid or acetone, and there is good reason for believing that it is not the acid of which Dr. Sternberg speaks. It is true that in some cases of diabetic coma the administration of sodium bicarbonate apparently is beneficial, but, as a rule, this treatment fails. Dr. Herter has shown most admirably that there is no constant relation between the amount of sugar and the acids that are excreted, and I am of the opinion that many patients with diabetes are injured by excessive nitrogenous feeding. The probability is that the poisonous agent, whatever it may be, comes from nitrogenous antecedents either in the food or in the tissue, and that it does not come from carbohydrates. I am very much interested in the large amount of potassium which Dr. Herter has found in his cases of diabetic coma. I infer that this finding indicates tissue disintegration, for I do not know of any other source from which so large an amount of potassium can come. I should like very much to have Dr. Herter's opinion on this point.

DR. HERTER: I would like to say in regard to the failure of the alkali treatment, that the organic acid is produced in such enormous quantities that we can hardly hope to remove more than a small portion of it. We do not know much about the formation of this acid, and there is a limit to the amount of

alkali we can administer; so in spite of the treatment the patient may enter a state of coma. I do not regard that as a valid objection to the theory, and do regard the not infrequent success of the alkali treatment as a very important evidence of the correctness of this view. At the same time I do not feel wholly committed as to the nature of the acid in the blood. Such evidence as there is points to oxybutyric acid far more strongly than to the amido acids.

I think there is something to be said in regard to the view just expressed on the giving of nitrogenous foods. It is extremely difficult to determine the origin of these acids, and experimental work has shown that while such acids may be derived from the proteid we have also to say that a considerable amount of ammonia comes from the same source, especially from meat: whether or not these influences balance each other I cannot say. As to the origin of the potassium, I have reached no conclusion. Perhaps Dr. Vaughan's suggestion is correct.

DR. PFAFF: I would like to make a few remarks in regard to the treatment of diabetes. It was suggested that too much stress was laid upon the treatment of diabetes by exclusive proteid diet. It was said that this was wrong, and that should a certain quantity of carbohydrates be added to the diabetic diet, less acetone and acid intoxication leading to coma would ensue. Of course, everybody knows by experience that there are diabetics who do not thrive on an exclusive proteid diet, and who, under such a *regime*, lose flesh constantly. In such cases it is imperative to add carbohydrates to the proteid diet. In spite of an increased quantity of sugar appearing in the urine, some of these patients stop losing flesh; existing gastrointestinal and nervous disturbances may disappear promptly, which could not be remedied by other means, and the patient may even increase in weight. But these observations do not change anything in the fundamental treatment of diabetics—*i. e.*, to limit their diet to exclusive proteid food and to add fat and carbohydrates to this diet after the patient has got rid of the sugar in his urine under exclusive proteid diet. That under proteid diet, with complete exclusion of carbohydrates, acetone and diacetic acid may disappear from the urine has been demonstrated to us more than once in the treatment of diabetes. In one case, a boy of fourteen years, the diacetic acid and acetone which were present under the unrestricted mixed diet disappeared only after rigid treatment of proteid diet carried out strictly for a few months. In this case the sugar also disappeared rather slowly, but under strict diet the sugar disappeared first, and then the acetone and diacetic acid vanished completely from the urine after the diet was followed for a few months, and the patient gained twenty pounds.

In another case the bad effect of carbohydrates in the treatment of diabetes was neatly demonstrated. A seamstress, about forty years old, suffered from a very severe attack of diabetes. Even under the strictest diet the urine contained about 2 per cent. of sugar, besides a large quantity of acetone and diacetic acid. When the patient came first under observation examination of her urine showed also a large quantity of albumin and many hyaline,

granular, and fatty casts. Under strict diet the sugar was decreased, but acetone and diacetic acid never disappeared, even after months of treatment. The subjective symptoms of the patient improved considerably, and she was able to resume her ordinary work for a few months. Re-examination of the urine showed at the time of treatment a marked improvement. Albumin was present only in a slight trace, and scarcely any casts were found. As soon as the patient was allowed sixty grams of bread per day the albumin increased considerably, and hyaline, granular, and fatty casts reappeared in large numbers. The quantity of sugar in the urine increased, of course, also. As soon as the bread was excluded from her diet for a few days or a week the albumin in the urine nearly disappeared, and the casts also. The most probable explanation of this observation was that the small quantity of carbohydrates in the food had increased the quantity of sugar present in the urine, and had so caused local irritation of the kidneys. In our endeavor to increase the patient's diet we tried in this case repeatedly to add the same quantity of bread to the strict diet, but always with the same results. The urine showed each time the same pathologic changes—increased albumin and presence of a large number of casts, and the patient felt worse for it. That exclusive proteid diet is not the cause of acetone and diacetic acid, but that other factors may account for their presence has lately been demonstrated by different authors. They have proved that an increased quantity of fat in the diet in the presence of a comparatively small quantity of proteids may cause acetonuria. It would seem, therefore, that under certain conditions we have to decrease the quantity of fats in the diet of diabetics to avoid complications. On this point very little stress has been laid in the treatment of diabetics. It is not impossible that the large quantities of acetone found in the urine of diabetics when taking large quantities of fat may disappear when the ingestion of fat is reduced. In one observation, where the patient became sugar-free, large quantities of acetone were present in his urine under unrestricted proteid-fat diet, plus 150 grams of bread per day. This acetone disappeared from the urine slowly when the patient diminished the ingestion of fat. We have made only this one observation, and from it it is not permissible to draw any conclusions. But it would be very important to know if in similar cases the reduction of fat ingestion is followed by diminished excretion of acetone.

As I remarked already, in this case under observation, the acetonuria was only very slowly affected by the change of the diet, but finally the quantity of acetone in the twenty-four hours' urine became normal.

The fact found by Drs. Joslin and Herter, that the quantity of potassium is increased in the urine, is very interesting. Normally, the solid tissues of our organ contain more potassium than the liquid tissues—such as blood and lymph. The increased quantity of potassium excreted in the urine may possibly be explained by the fact that the pathologic changes in diabetes are going on mainly in our solid tissues. Too little, however, if anything, is known of the true causation of diabetes, and it would be too hasty to draw any conclusion from this interesting observation of an increased potassium excretion.

THE URINE AS A SOIL FOR BACTERIAL GROWTH.

By WILLIAM HALLOCK PARK, M.D.,
OF NEW YORK CITY.

THE exact tests of the degree of acidity or alkalinity present in a number of samples of urine revealed such marked differences in the amount of alkali or acid present that it seemed to me it would be of interest to determine how far the reaction of the urine determined, whether it was to be a favorable or unfavorable soil for the growth of the bacteria commonly met with in cystitis, pyelitis, or bacteriuria.

In all, 45 samples of urine have been tested. These specimens were obtained in one-third the cases from healthy persons. The others were from persons suffering from various diseases and taking various drugs. For the acidity tests I am indebted to Mr. J. P. Atkinson.

In every case the urine was drawn in as clean a manner as possible and then immediately filtered through a Chamberlain filter into test-tubes, each test-tube containing about 3 c.c. The reaction of the urine was tested, also its sterility, and then inoculated with the organisms to be tested. From fresh twenty-four-hour bouillon cultures watery dilutions were made, and then from each variety one set of tubes received from 50 to 500 organisms, the other set from 50,000 to 500,000. When no growth took place, in the tubes inoculated with the larger number of bacteria from any culture, a large loopful scraped from a fresh nutrient agar culture was added. All inoculated specimens of urine were left ninety hours at blood-heat and examined daily.

As many of the specimens of urine were practically duplicates, so far as the tests were carried, although from various persons, the details of the tests are given for only 11 urines, which, when taken together, give a fair picture of the whole 45.

TABLE I.—The development of five varieties of bacteria in the urine of eleven different individuals, the specimens of urine being arranged according to their acidity.

	Characteristics of persons from whom urine was taken.																							
	1		2		3		4		5		6		7		8		9		10		11			
	Endocarditis‡ 200 grains sodium sol. daily.		Poor health; no drugs.		Healthy.		Chronic gonorrhea and cystitis.		Acute nephritis, albumin in urine.				Scarlet fever.		Healthy adult.		Chronic intestinal putrefaction.		Nephritic.		Diabetic.			
Organisms	—	—	+	—		+	+		+		+	+	+	+	+	+	+	+	+	+	+	+		
	2	14	2	10	8	0	12	1	12	1	19	9	36	14	49	38	61	29	63	21	70	38		
	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**		
Gonococcus	—	—	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Streptococcus	—	—	—	—	+	—	+	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—		
Staphylococcus	—	—	—	—	+	—	+	+	—	+	+	+	+	.	—	—	+	—	+	—	+	—		
Bac. coli com.	—	—	—	—	+	.	+	+	—	+	+	+	+	.	—	—	+	—	+	—	+	—		
B. proteus vulgaris	—	—	—	—	+	+	+	+	+	+	+	+	.	+	—	—	—	—	—	—	—	—		

NOTES. ‡ The acidity in the first column are to phenolphthalein, in the second to litmus; — indicates alkalinity, and + acidity in number of c.c. of normal hydrochloric acid solution or normal sodium solution required per litre to neutralize the urine.

** = growth when between 10 and 100 organisms were added to 1 c.c. of urine.

* = growth when over 10,000 organisms were added to 1 c.c. of urine.

— indicates no growth under the same conditions.

A study of this table indicates that the reaction of the urine had much to do with its suitability for bacterial growth; an examination of the whole 45 urines shows this even more clearly. The reaction of the urine influenced the different varieties of bacteria in very different degrees.

Gonococcus. A number of cultures derived from cases of acute and chronic gonorrhea were employed, and in no case did any visible growth occur in any urine except with one variety, which was derived from a case of chronic cystitis with a history of twenty-years' duration, in which for over a year we had obtained gonococci. Even here the growth was very slight. This gonococcus grew on ordinary nutrient agar containing 2 per cent. of peptone.

The only urines in which this gonococcus grew were neutral or nearly neutral to litmus and slightly acid to phenolphthalein (No. 3).

That the gonococcus rarely occurs free in urine is a well-known fact, and is apparently due, in part at least, to its inability to grow in it.

The streptococcus grew readily, as a rule, in the slightly alkaline, neutral, and very slightly acid urines. Over one-half of the urines were too acid for its growth (Nos. 6 to 11).

The staphylococcus grew well in the neutral and moderately acid, but poorly in the more acid urines, and then only when large numbers of organisms were added (Nos. 8 to 11).

The colon bacillus grew much as the staphylococcus. The bacillus proteus vulgaris did not grow at all in the most acid. The changes in reaction produced by the bacteria were as follows: None of the varieties produced appreciable acid except in cases of diabetes, where acid was produced by the colon bacillus. This was due to the fact that, as a rule, urine contains no appreciable quantity of any substance which is capable of undergoing an acid fermentation.

The production of alkali, mainly by the decomposition of the urea, was very rapid and marked in the case of the bacillus proteus vulgaris, so that a moderately acid urine became in eighteen hours intensely alkaline. The staphylococcus produced considerable alkali, but much less than the members of the proteus growth. The alkali produced by the growth of the colon bacillus was too slight in amount to have any appreciable importance in changing the reaction of the urine in the bladder. The same was true for the streptococcus.

In order to test the effect of acid substances in the urine, 1100 c.c. of neutral nutrient bouillon was divided into 11 portions. In 10 of these portions the most abundant acid salt of the urine, acid sodium phosphate, was added so as to make variations in acidity covering all met with in urine.

TABLE II.—Growth of varieties of bacteria common in urine in bouillon containing amounts of acid sodium phosphate ranging from the least to the greatest ever found in urine.

Organisms.	Acidity to phenolphthalein.										
	Neutral	10	+20	+30	+40	+50	+60	+70	+80	+90	+100
Gonococcus*	?	?	?	—	—	—	—	—	—	—	—
Streptococcus	+	+	slight	—	—	—	—	—	—	—	—
Micrococcus urea	+	+	+	+	+	+	—	—	—	—	—
Staphylococcus	+	+	+	+	+	— +	— +	— +	— +	— +	— +
Proteus vulgaris	+	+	+	+	+	+	— +	— +	— +	— +	— +
Pyocyaneus	+	+	+	+	+	+	+	+	+	+	+
Bac. coli com.	+	+	+	+	+	+	+	+	+	+	+
Bac. typhosus	+	+	+	+	+	+	+	— +	— +	— +	— +

* No visible growth, but gonococcus remained alive.
— + = growth only when a great number of organisms are added.

This table indicates that the acidity of the urine is in itself frequently sufficient to prevent a development of either the streptococcus or gonococcus in the urine. For the colon and pyocyaneus groups the acidity due to acid sodium phosphate would appear to never reach a grade sufficiently intense to prevent growth, although it might be sufficient to inhibit the rapidity of development.

Evidently other factors besides acidity are present to inhibit the growth of bacteria. Thus the reaction in sample 2 was satisfactory, and yet no bacteria would develop in it. Specimen 8 was less acid to phenolphthalein than 11, and yet the staphylococcus and colon bacillus grew when large quantities of the cultures were inoculated in 11 but not in 8. As to the nature of the substances other than acid salts which inhibit or prevent the growth of bacteria, no studies have as yet been made by us.

My thanks are due to Dr. Rose A. Bebb, assistant bacteriologist in the New York University and Bellevue Hospital Medical College, for testing the bacterial growth in many of the samples.

NOTES ON THE FEVER OF HODGKIN'S DISEASE; RECURRENT (RÜCKFALL) FEVER; EBSTEIN'S DISEASE.

By J. H. MUSSER, M.D.,
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Fever has long been observed as a symptom of Hodgkin's disease. It had usually been described as continuous. That other types are not uncommon the following notes will show. The type upon which we wish to lay most stress is that known as recurrent fever, the relapsing type.

In 1870 Murchison (*Transactions of the Pathological Society of London*, 1870, vol. xxi. p. 372) described the case of a girl of six years, who had had scarlet fever and whooping-cough. Shortly after the latter disease she developed fever, and from then until her death, ten months later, had regular paroxysms, recurring every four weeks, the maximum temperature being attained on the seventh day. During these attacks the lymph glands in the neck and axilla became enlarged and tender, and the heart enlarged slightly. During the intervals the patient had a ravenous appetite.

The family history was entirely negative. At the autopsy the glands were found enlarged and firm, and there were white nodules in the enlarged spleen, in the liver, and in the lungs, and general anemia of the tissues.

The microscopic examination showed the characteristic picture of lymphoma, and Murchison regarded the case as one of pseudo-leukemia, similar in all respects, save the paroxysms of fever, to one he had already reported. He was unable to find any similar case recorded in the literature, but recollected one in his own practice that had occurred in a girl, aged eighteen years, whose spleen and lymph glands were enlarged. Unfortunately she was under observation only a short time.

Nine years later Gowers (Reynolds' *System of Medicine*, vol. v. p. 306 *et seq.*, London, 1879), in his memorable article, described three types of fever as occurring in pseudoleukemia—continuous, alternating, and remittent. He reports no cases, but gives a chart of a case of the second type, and probably also had in mind Murchison's isolated case when mentioning this type. Except for this brief notice the symptom appears to have attracted no attention.

After another long interval a second case was reported by Pel (*Berliner klinische Wochenschrift*, January 5, 1885, vol. xxii., No. 1, p. 3) in connection with another of pseudoleukemia. The patient was a man, aged twenty-five years, who, in June, 1884, developed chills, fever, nausea, pain in the abdomen, and malaise. When first observed a few days later he was pale, the spleen was enlarged, and there were physical signs of acute bronchitis. From this time the temperature showed the following extraordinary course: Fever for eleven days, apyrexia for fifteen days, fever twelve days, apyrexia fifteen days, fever fifteen days, apyrexia fifteen days, fever thirty-two days, apyrexia nine days; fever and death from heart failure. During the last week there had been jaundice. No blood-counts apparently were made, but Pel states that the leukocytes were slightly increased, and that there was progressive anemia. At the autopsy the liver, spleen, and lymph glands were enlarged; there were none of the lesions of typhoid fever, although this disease had been suspected during life, and he therefore made a diagnosis of pseudoleukemia, and reports the case as such.

Two and one-half years after this Ebstein (*Berliner klinische Wochenschrift*, 1887, vol. xxiv. pp. 565 and 837) reported a case that had been most carefully studied and has been the cause of giving his name to the disease. Ebstein called it a case of recurrent (Rückfall) fever; or, as Osler puts it, "by the remarkable title of chronic recurrent fever, a new, infectious disease." The symptom attained the dignity of a disease.

The patient, a male, aged nineteen years, had had diphtheria and dysentery in childhood. In June, 1886, he first noticed malaise, headache, and loss of appetite, and pain of an intermittent character in the right side of the abdomen. In September of the same year the temperature records began. In two hundred and eleven days there were nine paroxysms of fever of an average duration of thirteen to

fourteen days, with afebrile intervals of ten to eleven days, making the intervals between the highest temperatures about twenty-four days. The maximum temperature was 40° to 41°, or a little more. The minimum temperature, 35.6° to 36°. During the attacks the temperature rose slowly, and sank rather suddenly. Often the defervescence was accompanied by sweating. At one time there was an attack of acute pleurisy, with exudation. The pulse and respiration varied with the temperature; the mind remained clear; the appetite was lost during the paroxysms, but became ravenous during the intervals. The feces and urine were normal, though the urea was slightly increased during the paroxysms. The spleen was enlarged, and became even larger during the febrile periods, but the lymph glands were not enlarged. Treatment had not the least effect. After the tenth paroxysm the temperature remained elevated for twenty-two days, then fell, but rose almost immediately, and the patient died five days later in collapse. In the last days there had been dyspnea, pleural effusion, anasarca, and a gangrenous bed-sore over the left trochanter. At the autopsy white nodules were found in the pleura; the bronchial and mediastinal lymph glands were enlarged, but not softened, and there were nodules in the spleen, liver, and kidneys.

He regards the case as one of hard, malignant lymphoma, but is not willing to include it among the pseudoleukemias, unless a sharp distinction be drawn between the febrile and afebrile forms.

While the observations upon this case were being completed, Pel (*Berliner klinische Wochenschrift*, vol. xxvi., No. 35, p. 644) had reported two additional cases which had already been published in a Dutch journal.

The first was a sea officer, thirty-two years of age, who had spent a considerable amount of time in the Dutch East Indies, where he had frequent attacks of malaria, inflammation of the liver, and dysentery. Upon his return to Europe he felt ill, and took several cures. These were not thoroughly successful. From March, 1884, he began to notice slight attacks of fever. He was under observation from May of the same year. From this time he had regular attacks of fever, lasting ten or twelve days, alternating with periods in which the temperature was normal or subnormal. There was progressive anemia and cachexia. Death occurred on January 12, 1885. A short time before the patient had developed hematogenesis icterus, had had per-

sistent singultus, and died apparently as a result of cholemia. At the autopsy the spleen and liver were found to be greatly enlarged, and there was also considerable hard enlargement of the mesenteric lymph glands. Microscopically the changes found were focal hepatitis.

The second case was also a man, forty-one years of age, who had been a sailor, and had been in the East Indies, where he had contracted yellow fever. He had never had malaria or dysentery, and his family history was entirely negative. The attacks of fever commenced in October, 1883. The febrile periods lasted about fourteen days, and the afebrile periods from fourteen to twenty-one days. The spleen, liver, and lymph glands were enlarged; there was progressive anemia; the skin was grayish-yellow, but there was no jaundice until just before death. When the blood was examined the red blood-cells were normal, and there was no leukocytosis. At the autopsy the lymph glands were enlarged and hard, and there were grayish-yellow nodules in the liver, spleen, and kidneys. It was particularly mentioned that not a trace of tuberculosis was found in the lungs.

With the publication of these cases and the completion of Ebstein's paper the early history of this symptom-complex may be regarded as complete. The clinical course is so characteristic that it was given a place almost at once as a clearly defined process. Since then additional cases have been recorded, but practically nothing has been added to our knowledge. The cases which we have been able to collect from the literature, which appear to be all, are as follows:

Hanser (*Berliner klinische Wochenschrift*, August 5, 1889, vol. xxvi., No. 31, p. 692). The patient was a male, without any important features in the family or previous history. On December 2, 1882, he was taken sick with pain in the abdomen. When examined a tumor-like formation was found in the abdominal cavity, which was somewhat tender, and there was dilatation of the left ventricle of the heart. He had attacks of fever lasting from ten to twelve days; the temperature would rise slowly to about 40°. Usually there was some sweating in the beginning of the attack, and during it the pulse increased in frequency, the dilatation of the left ventricle became more pronounced, and there was moderate loss of weight. The intervals averaged about ten days in duration, although occasionally, especially toward the end, when the fever was moderately irregular, they only lasted one day. The blood was normal throughout the entire course

of the case. Four weeks before death the patient developed anasarca. Death occurred as the result of exhaustion. An autopsy could not be obtained.

Völckers (*Berliner klinische Wochenschrift*, September 9, 1899, vol. xxvi., No. 36, p. 796). The patient was a man, thirty years of age, who had had syphilitic infection. In October, 1884, he had some gastric disturbance, with pain located just to the left of the umbilicus, and there was slight fever. He was given sodium iodid, and improved, but, after severe physical exertion, he had a renewed attack of fever, and a tumor was recognized, situated to the left of the spinal column and extending from the umbilicus into the pelvic cavity. From this time he had the characteristic febrile movement. The periods of pyrexia lasted fourteen days; the periods of apyrexia from seven to eight days. The temperature rose and fell slowly, and during the intervals was not subnormal. During the febrile attacks the patient had loss of appetite and gastric disturbances, characterized by nausea and occasional vomiting. Toward the end of the attack the fever became quite irregular, but even then showed a tendency to the recurrent type. At the autopsy a tumor was found attached to the periosteum of the lumbar vertebræ, and the retroperitoneal lymph glands were enlarged. The tumor was diagnosed as a fusocellular sarcoma, with peculiar areas of degeneration. Bands of connective tissue passed through it in various directions. The bloodvessels were distinctly sclerotic. The tumor was composed of two types of cells, the epithelium and lymphocytes. Völckers regards it as of an infectious type.

Although there is little doubt that this case belongs to the group of cases we are describing, there seems to be more doubt in regard to the case of Hammer (*Virchow's Archiv*, 1894, vol. cxxxvii. p. 280). The patient was a man, forty-one years of age, a miller by occupation, who had had an attack of pericarditis at the age of thirty-six years. He had also suffered from time to time with articular rheumatism and pains in the lumbar region. On February 6, 1891, he had a sudden attack of headache, with pain and tenderness in the chest. For nine months he had recurrent fever, somewhat irregular, the periods of pyrexia lasting from one to six days and the periods of apyrexia from one to twelve days. In the early part of the disease he had an attack of acute pleurisy, which did not recur. Shortly

after the first symptoms pains developed in the knees and rapidly involved the whole bony system, especially the spine. There was some edema over the spinal column. The blood showed at first a moderate poikilocytosis; later there was a slight leukocytosis, and there was progressive anemia. Death occurred on November 27, 1892, nineteen months after the appearance of the first symptoms. At the autopsy the bones were found hardened throughout the body. There were numerous small nodules on the serous membrane, and the lymph glands were enlarged. Microscopically the bone tumors presented the picture of multiple myeloma. The tumors of the serous membranes and of the glands were composed of round cells.

A typical case, clinically, is the one which was reported by Askanazy (*Zeigler's Beiträge*, 1888, vol. iii. p. 413). The patient, a woman, thirty-two years of age, both of whose parents were healthy, and who had herself been healthy in childhood, was attacked with a severe cough, thirst, and fever. There was a slight greenish-white, tenacious expectoration; there was also some gastric disturbance, with nausea and vomiting. There was pain in the right side of the abdomen and moderate psoriasis of the body. The nutrition was poor, and a tumor could be detected in the right supraclavicular fossa, which was soft and not painful. The heart was normal. The patient was under observation nineteen days. During this time there was for four days a temperature normal in the morning and slightly elevated in the evening; then for three days a temperature elevated morning and evening; then for two days a temperature normal in the morning and considerably elevated in the evening, and for the last nine days persistent pyrexia, with temperature usually exceeding 39°. There was frequent diarrhea, the sputum did not contain tubercle bacilli, and the urine was normal. The patient died of exhaustion and edema of the lungs. At the autopsy the thoracic glands were found greatly enlarged; the lymph glands at the hilum of the spleen were also increased in size; the lungs were normal. Microscopic examination of the glands showed the characteristic changes of tuberculosis, and tubercle bacilli were found in great numbers.

The author believes that possibly the case of Ebstein was also one of tuberculosis, although tubercle bacilli were not found, and thinks it not unlikely that Pel's case was of similar nature. He concludes that there are cases that give the clinical picture of pseudoleukemia,

and yet, as a matter of fact, are due to tuberculosis of the lymph glands.

Renvers (*Deutsche medicinische Wochenschrift*, September 13, 1888, p. 753) reports the case of a man, aged twenty-one years, who in childhood had had smallpox, but was otherwise healthy. In 1887 he suffered from time to time with colic-like pains in the abdomen. When admitted to the hospital, on October 20th of that year, it was found that the spleen and liver were enlarged and somewhat tender. While in the hospital he had repeated attacks of fever, lasting from eight to eleven days, in which the temperature usually exceeded 40°. This alternated with attacks in which the temperature was normal or slightly below, lasting from eight to fourteen days. During these attacks the spleen and liver increased distinctly in size; the retroperitoneal lymph glands gradually enlarged during each attack, until they formed a tumor-like mass to the left of the umbilicus. There was no leukocytosis, but a progressive anemia and cachexia. The appetite was lost during the febrile periods, but the patient ate ravenously during the intervals. The diazo reaction was constant throughout the disease. An autopsy was secured, and the changes characteristic of lymphosarcomatosis were discovered. Renvers regards the case as a form of infectious pseudoleukemia.

Seebohn (*Jahrbüch. der Hamburgischen Staats-krankenanstalten*, Leipsic, 1892, p. 65) reports an extremely doubtful case. A woman, eighteen years of age, who had frequently suffered from anemia, in June, 1889, had severe pain in the left thorax, extending to the left shoulder. This disappeared for a year, and then recurred in the same situation. On July 5, 1890, she had chills and fever, followed by headache. When examined, signs of tumor just behind the left side of the sternum were discovered. This tumor was tender on pressure. The thyroid glands were much enlarged. The fever continued until July 16th; there was then an intermission for three days, when the temperature rose again, and the patient died. At the autopsy a lymphosarcoma of the thymus was found, involving the neighboring lymph glands.

Kisset (*Vratch*, 1894) points out the frequent occurrence in children of the above-mentioned type of fever.

Osler refers to it in his text-book, and states that he has seen three cases.

Quite recently the symptom was more firmly established as a disease, Pinkus being the godfather. He terms the ailment "Chronic Relapsing or Recurrent Fever" (Ebstein). Briefly his paper is as follows:

Pathologic Anatomy. There is present a malignant growth in some lymphatic organ (glands, spleen, or bone-marrow). Hammer says sarcoma. Often a lymphosarcoma or a sarcoma-like round-celled tumor is found.

Clinical Relations. The disease has the symptoms and signs of a pseudoleukemia with intermittent fever. A period of one to three weeks of fever alternates with an apyretic period of the same length. It must be differentiated from similar cases of malaria, which are also cured by arsenic, and not affected by quinine. A peculiar tubercular lymphoma may give the same clinical picture, while the tumors may be of spindle and epithelioid cells (Schottelens in Völcker's case). The pathologic anatomy and the blood histology have not been sufficiently worked out to decide definitely in regard to the nosology of this disease.

In 1898 Sternberg (*Archiv für Heilkunde*, vol. xix. p. 21) reported fifteen cases that had been diagnosed as pseudoleukemia, and in which he had been able to make a careful histologic examination of the tissues. The clinical histories are entirely inadequate, and it is impossible to state how many of them belonged to the category of Ebstein's disease. In the eighth case, however, it is stated that the clinical diagnosis was pseudoleukemia, with recurrent fever. In this case the histologic examination showed the presence of miliary tuberculosis, involving especially the liver and kidneys. In the lungs there was the typical picture of cheesy pneumonia, with miliary tuberculosis in the lymph glands, and numerous large cells. Many of them had undergone extensive cheesy degeneration. Nearly all of the other cases showed extensive tuberculous changes, and Sternberg expressed the opinion that in the majority of cases pseudoleukemia is really a tuberculosis of the blood-forming apparatus. He thinks that in all likelihood this is especially true of the cases with recurrent fever.

In cases of pseudoleukemia without tuberculosis the hyperplasia and peculiar structure of the lymph glands leads him to believe that it is not impossible that we have really a form of multiple sarcoma. He thinks, however, that there is a peculiar form of tuberculosis of the lymphatic apparatus which is essentially characterized by the fact

that a more or less peculiar form of granulated tissue is produced in these structures that is apparently characterized by its great rigidness in their large structures. Sometimes there will be in the course of the disease a typical tuberculous granular tissue, and he urges particularly against the diagnosis of pseudoleukemia before a careful histologic examination of the tissue and before the inoculation of animals has been performed.

Ehrlich and Lazarus have recently discussed the literature of this subject in their article on anemia in Nothnagel's *System*. They regard it as a peculiar form of pseudoleukemia characterized by the recurrent type of fever. It is often associated with splenic tumor, and occasionally lymphomata appear that resemble round-celled sarcoma; in fact, the anatomic picture resembles that of lymphosarcoma or Hodgkin's disease.

Among the etiologic factors malaria should be reckoned; at least it sometimes produces a clinical picture that is identical, with the exception that the patient recovers upon arsenic.

The authors regard the occurrence of tuberculosis, which has caused Sternberg to express the idea that pseudoleukemia is merely a form of tuberculous lymphoma, as usually accidental. They are not certain that it is justifiable to regard cases of pseudoleukemia with recurrent fever as a peculiar form of disease, but prefer to await further investigations.

Kost (*Jahrbücher der Hamburgischen Staats-krankenanstalten*, 1889, No. 1, p. 174) reports three interesting cases. The first, a boy, aged seven years, was admitted to the hospital on March 31, 1889, with a history of having had an acute sickness for fourteen days, during which time he had had headache, felt weak, and lost his appetite. There was slight diarrhea and apparently fever. The patient was pale; poorly nourished. There were physical signs of bronchitis of the left lower lobe; the spleen was enlarged and palpable; the cervical lymph glands were considerably enlarged. A diagnosis was made of typhoid fever; the temperature was 39°. On June 2d temperature was normal. Seven days later the spleen was smaller, patient had increased in weight; appetite was ravenous. On June 14th there was slight elevation of temperature, which increased and persisted until the 20th, when it fell suddenly. During this afebrile period the patient did not improve as much. On July 1st

there was again gradual rise of temperature; spleen enlarged; the other symptoms were the same. On July 8th the temperature fell suddenly. This continued, the attacks of fever lasting from seven to twenty-four days (the last), the intervals from three (the last) to seventeen days. The patient died in the ninth attack, which lasted one day. The condition was characterized by the rapid progressive anemia, the slight edema of the extremities, the enlargement of the spleen and lymph glands during the febrile attacks. Toward the end there was distinct ascites. The blood showed toward the end a marked leukocytosis (100,000), which rapidly increased until there were 2,700,000 and 3,200,000 whites. The hemoglobin was greatly reduced. At the autopsy the spleen and lymph glands were enlarged. There were numerous, in part confluent, nodules surrounding the bloodvessels, and there were numerous scars in the kidneys. Nodules similar to those in the spleen were found in the liver. The bacteriologic investigation consisted in various cultures on various media, and the implantation of fragments of tissue in the anterior chamber of a rabbit's eye and in the peritoneal cavity of guinea-pigs gave no results. The histologic examination of the tissues showed that the tumors were really small sarcomatous masses, and in all probability were metastatic; they did not resemble leukemic infiltration.

The second case (a man, aged thirty-five years) was without previous history, family or otherwise. He had noted in the summer of 1889 that the left foot enlarged on long standing. The previous winter he had noticed enlargement of the inguinal glands on both sides. In the course of time these gradually enlarged, and he had an attack of erythema in the right thigh, and fever, lasting three days. He continued to vary from good to worse for some time. Enlargement occurred in the cervical glands, and in April, 1890, he had another attack of fever, lasting five days. When brought to the hospital the temperature was slightly above normal, the axillary and inguinal glands were enlarged, and there was a tumor about the size of a fist in the epigastrium. On May 22d he had an elevation of temperature to 40°. There was erythema in the right thigh. On the 25th the temperature fell to normal, rising again on the 30th, and became normal on June 2d. On June 18th a tumor appeared on the right side of the inferior maxilla. This diminished somewhat in size, and on the 22d a tumor appeared in the fourth intercostal space, and upon the back at the

level of the first dorsal spine. There was neither peptone, propeptone, nor acetone in the urine. The patient is still under observation.

Finally, the case of a boy, sixteen years of age, who had always been weakly. He had noticed a swelling in the region of the right hip in 1883–84. When admitted, February 28, 1894, the temperature was slightly elevated, the right hip was diffusely swollen, and there was some limitation of movement. The patient had a remittent fever, which after an operation still persisted, was associated with enfeeblement of power, and finally death. The tumor of the hip was a sarcoma, and there was sarcomatous infiltration of the neighboring lymph glands. The author also reports five cases of carcinoma of the stomach, in all of which fever had been a prominent symptom. He concludes as follows: Malignant tumors, sarcomas or carcinomas, may cause considerable elevation of temperature. This is, however, the exception. The type of fever may be remittent, intermittent, or recurrent. The cause of the fever may be the absorption of septic material as the result of the breaking down of the tumor. Other hypotheses are the peculiar type of the temperature regulating apparatus of the individual, the intermittent type of the invasion of the metastases, the localization of the tumor in the organs concerned in the formation of blood.

A very similar case has recently been reported by Witthower (*Münchener medicinische Wochenschrift*, February 5, 1901, p. 224). The patient, a woman, twenty-four years of age, had been admitted to the hospital, supposed to be suffering from influenza. She was well-nourished, and apparently had no disease. The physical examination disclosed the presence of a pleural exudate on the left side. There was moderate fever, which continued until this was aspirated, eight days later. On April 22d the fever recommenced, and continued until May 11th, when a second aspiration was practised. For five months after this the patient suffered from periodical attacks of fever, lasting three days, separated by intervals in which the temperature was normal or slightly below, lasting three or four days. This fever was absolutely rebellious to treatment. Malarial parasites were not found, and tubercle bacilli were absent in the sputum. In the last six weeks of life the patient became slightly cyanotic, and there was visible pulsation of the cervical vessels. The patient developed symptoms of stenosis of the bronchi, there was paralysis of both vocal cords,

and she died on October 7th of exhaustion. At the autopsy a round-celled sarcoma was found in the posterior mediastinum, which had invaded the auricles of the heart and the right lung. There were multiple abscesses on the right lower lobe, and passive congestion of all the organs. Witthower believes that this extraordinary temperature was due to the introduction, at regular intervals, of the products of disintegration, the toxins or similar material into the circulatory organs.

We have had the opportunity of studying two cases which are worthy of consideration. Neither of the cases came to autopsy. The first case was one of Hodgkin's disease with undoubted tuberculosis, although tubercle bacilli were not found in the discharges. The second case was also one of so-called Hodgkin's disease, in which the clinical course was that of tuberculosis, such diagnosis made positive by the finding of tubercle bacilli in the sputum.

CASE I.—This case was observed in 1891 and 1892. The patient, a boy, aged sixteen years, was admitted to the hospital on November 13, 1891, with the following history: He had been sick for five or six months with a condition diagnosed by the attending physician as malaria. During this time he had been unable to work, and had had occasional chills, irregular pains, and loss of strength and appetite. Previous to this he had had no sickness. On November 27th he felt much worse than usual, was feverish, and had a profuse hemorrhage from the nose. From this time the fever continued and he felt very weak. Upon admission the temperature was 105°; pulse 120, full, regular, and compressible, and respiration 27. There was slight hebetude, some gurgling and tenderness in the right iliac fossa; the spleen was enlarged, but the abdomen was not distended. The heart-sounds were clear, the lungs normal, and the post-cervical glands on the left side were palpable. From the time of admission the temperature steadily and slowly declined, and on the morning of December 3d was normal. The following night it reached 96°; the pulse had dropped to 64, with good volume. From this time the temperature continued subnormal until December 12th. The appetite improved, he slept well, and felt much brighter. There was some constipation. On the 12th the temperature began to rise, and in twenty-four hours reached 104°. The axillary and cervical glands became considerably enlarged; the pulse was full and soft, and reached 95. The stomach became irritable, and the patient vomited, particularly after the administration of quinine. The appetite was lost, but the patient did not complain, and presented absolutely no symptoms to account for the rise of temperature, which ranged from 103° to 105°, while the pusle was 110 to 120; the respirations varied from 24 to 30. The patient had no cough, did not complain of pain, and the lungs were clear; there was slight yellowing of the skin, and very

pronounced emaciation. On December 21st the temperature steadily declined, and reached normal at 3 P.M. It then became subnormal, and remained so until January 1st. From this time the swollen glands in the neck and axilla diminished in size. The urine contained some bile and a distinct trace of albumin, but there were no casts. On January 2d the temperature began to rise gradually, and on the 4th had exceeded 103°. The lymphatic glands at the angle of the jaw and the post-cervical glands enlarged rapidly during this attack, and the glands in the groins and in other parts of the body became palpable. The tongue was coated; the appetite remained fairly good; the patient complained of no pain, and slept well. There was a soft murmur, systolic in time, at the base of the heart. On January 6th the stomach again became irritable, the patient vomited several times a day, and was constipated. Slight icterus reappeared on this day. On January 9th the temperature again commenced to decline, and reached normal in twenty-four hours. It then became subnormal and continued from 94° to 97° until the 14th, when it rose to 97°. During this period the pulse dropped to 70, appetite became ravenous, and the patient rapidly gained in weight; the jaundice cleared slowly, the glands in the neck decreased considerably in size, and the patient seemed in every way improved. As a rise of temperature was expected, he was given quinia bisulphate, 5 grains every three hours, on January 19th. In spite of this, the temperature again rose and reached 104°; it then dropped again below normal. On February 1st the patient passed into the hands of another service. The temperature was noted as elevated on the 12th. It was evidently of short duration, as it was stated that it was easily controlled, and the patient was discharged, improved, on the 19th of that month. He was readmitted almost immediately in a state of collapse, with weak, rapid pulse, subnormal temperature, and enlarged and tender spleen. On March 4th the temperature rose to 102°, and subsequently reached 106° On the 11th it was 102.4°; the patient was exceedingly weak and the pulse thready. On the 18th the temperature was again subnormal, and the patient seemed stronger. It remained down for fourteen days, and then suddenly rose to 104° on March 25th. On April 1st the patient had a severe attack of epistaxis, and on the 8th it was noted that the temperature was subnormal and the patient very weak. He was discharged from the hospital on April 9th.

After leaving the hospital we learned the patient lived just one month, dying on May 9, 1892. During this month he grew rapidly weaker, and the lower part of the body was said to be paralyzed. There did not seem to be any fever, although the temperature was not taken. The patient became extremely jaundiced, but had no vomiting, nose-bleed, or edema. On the day of his death he complained of severe pains in the knees and feet. His appetite had been failing, and, although he was depressed, his mind was clear. No autopsy was performed.

During the course of the case the diagnosis was exceedingly uncertain. At first it was supposed to be typhoid fever, as was Pel's first case. Of course,

the Widal reaction was not known at that time. It was then diagnosed as malaria. Investigation was made for the plasmodia of malaria, but they were not found. The blood was frequently examined for the spirilla of relapsing fever, but the results were always negative. Counts were made with the red blood pipet, which showed reduction of the red blood-corpuscles, and no obvious leukocytosis. Quinine was used very freely at various times, but often seemed to cause vomiting, and had to be discontinued. It had absolutely no influence upon the temperature, and the same was true of cold sponges and the coal-tar antipyretics which were occasionally used.

The case may be enumerated as follows. Recurrent fever of the following course:

Febrile period—November 27, 1891, to December 3, 1891 (six days).
Afebrile period—December 3, 1891, to December 12, 1891 (nine days).
Febrile period—December 12, 1891, to December 21, 1891 (nine days).
Afebrile period—December 21, 1891, to January 1, 1892 (eleven days).
Febrile period—January 1, 1892, to January 9, 1892 (eight days).
Afebrile period—January 9, 1892, to January 20, 1892 (eleven days).
Febrile period—January 20, 1892, to January 30, 1892 (ten days).

From the subsequent notes it is known that the temperature was subnormal on February 4th, that there was a transient rise just before the 12th, and that it was normal on the 19th. The next recorded febrile period commenced on March 4th, and continued on the 11th, but had ceased some time before the 18th. The afebrile period now lasted fourteen days, when, on the 25th, the temperature again rose to 104°, but on April 8th the temperature was again subnormal.

This case is remarkable for the number of paroxysms that were observed, and for their extreme regularity. During the paroxysms the glands in the neck and maxilla became swollen, and a heart-murmur developed. The patient had impairment of appetite, nausea, vomiting, and emaciated rapidly. Toward the end of the attack there was slight jaundice and bile in the urine. During the interval the swelling of the glands subsided, the appetite returned, the patient ate ravenously, and increased in weight. Death occurred as a result of the progressive cachexia, with the usual terminal icterus.

CASE II. *Hodgkin's disease; lymphatic, pulmonary, pleural, and meningeal tuberculosis; recurrent fever of more than six months' duration; death from tuberculous meningitis.*—J. C. W., aged fifty-nine years, married; merchant and capitalist. Active in business life; nervous temperament; moderate in the use of tobacco and stimulants. Never robust; subject to attacks of "biliousness" every two or three months.

Family history of tuberculosis very marked; no other inherited tendency.

Present illness of five years' duration. At first adenitis and asthenia; cervical, axillary, and inguinal glands involved. At the end of two years considerable return of strength, with diminution in size of the glands, but not of the spleen. The cervical and inguinal nerves entirely disappeared.

In 1899 had slight cough, but no physical signs of tuberculosis. In the autumn of 1900 failed rapidly, and in October fever began. It continued immoderately, and was recurrent or relapsing in type. In December, 1900, pulmonary tuberculosis developed. In February there was a large serous effusion in the left pleura. In May cerebral meningitis set in.

The Blood. Opportunity to make many examinations was not permitted. February 24, 1898: Hemoglobin, 71 per cent.; red blood-corpuscles, 4,778,500; white blood-corpuscles, 3688; polynuclear, 58.8 per cent.; eosinophiles, 12.7 per cent.; small lymphocytes, 21.04 per cent.; large lymphocytes, 13.77 per cent. April 6th: Hemoglobin, 82 per cent.; red blood-corpuscles, 5,913,280. October 6th: Hemoglobin, 70 per cent; red blood-corpuscles, 3,335,000. February 3, 1899: Hemoglobin, 105 per cent.; white blood-corpuscles, 9000; polynuclear, 42 per cent.; mononuclear, 12 per cent.; large lymphocytes, 6.5 per cent.; small lymphocytes, 4 per cent.; eosinophiles, 17 per cent.; transitional 14.5 per cent.; myelocytes, 3 per cent. October 23, 1900: Hemoglobin, 55 per cent.; red blood-corpuscles, 3,940,000; white blood-corpuscles, 4000; polynuclear, 54.50 per cent.; small lymphocytes, 31 per cent.; large lymphocytes, 25 per cent.; transitional, 3.25 per cent.; eosinophiles, 10.75 per cent.; mononuclear, 25 per cent.

Lymphatic Glands and Spleen. At first the adenitis was general; later the glands diminished in size; then they enlarged, to decline again. During the occurrence of the fever each paroxysm was preceded by pain in the inguinal glands of the right side. The patient could always predict a paroxysm. During the last six months of his illness progressive atrophy of all the glands took place. The *spleen* was enlarged and prolapsed. It never regained its normal size, although it was not enlarged to the same degree, because of the general atrophy, the last six months of life. The diagram shows the position and shape. The liver was enlarged two fingers' breadth upward and to the same extent along the lower margin; it was hard and often painful.

The Gastrointestinal Symptoms. They were not unusual. There was some anorexia always, but during the course of the fever it was complete. Food was repugnant, and for two or three days at a time nothing would be taken. Constipation, alternated with diarrhœa; the former was more prevalent. Vomit of fluid, as in chronic gastritis, occurred during the febrile paroxysms, especially in the first period of the fever.

The Pulmonary Symptoms. Cough and dyspnea occurred in due time. During 1900 there was some cough. In December, 1900, there was bronchitis, and tubercle bacilli were found in the sputum. In January consolidation of the upper part of the lower right lobe was found. In March there was a left pleural effusion; the fluid removed by aspiration was negative for tubercle bacilli. General tuberculosis of the lungs ultimately prevailed.

The Heart and Bloodvessels. The heart in the late periods (three months) dilated, and murmurs developed in consequence. The pulse was always of low tension.

Urine. October 30, 1900. Specific gravity, 1010; albumin, trace; sugar, 0; occasional granular casts.

22*d.* Red amber; specific gravity, 1020, acid; albumin, trace; sugar, 0; several granular casts; epithelial cells.

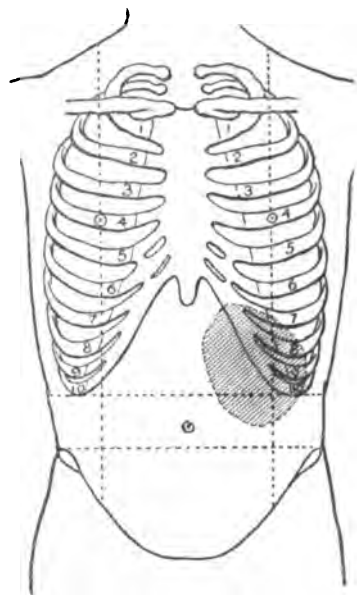
November 14*th.* Amber; specific gravity, 1010, acid; albumin, trace; sugar, 0; few hyaline casts.

26*th.* Specific gravity, 1020; albumin, trace; sugar, 0+; small hyaline and granular casts.

28*th.* Specific gravity, 1020; albumin, trace; sugar, 0; amorphous urates.

December 3*d.* Specific gravity, 1012, acid; albumin, trace; sugar, 0; oxalates of lime; a hyaline cast.

14*th.* Specific gravity, 1018; albumin, trace; a hyaline cast.



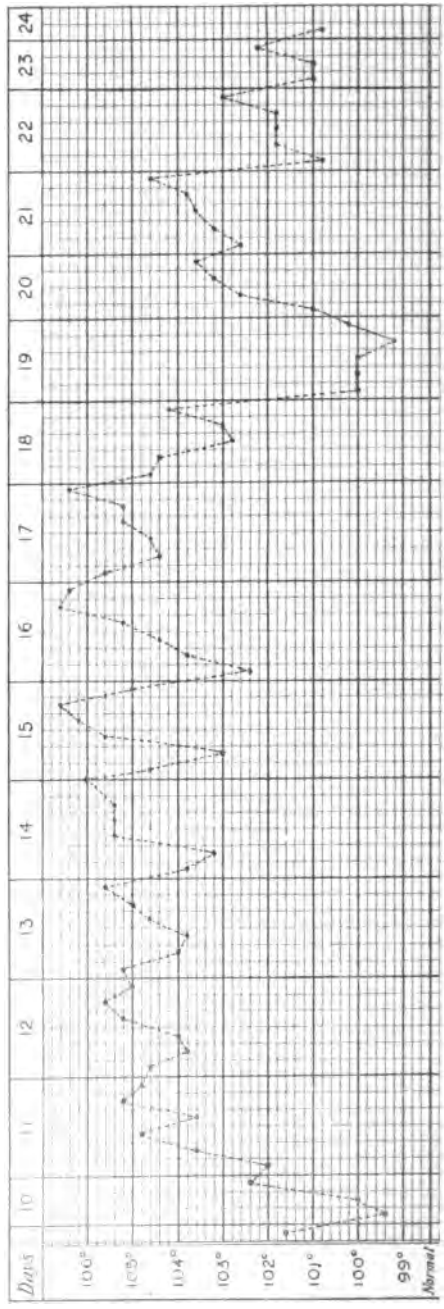
18*th.* Twenty-three ounces in twenty-four hours; dark amber; specific gravity, 1030, acid; albumin, trace; sugar, 0; urates; amorphous; occasional hyaline casts.

January 23, 1901. Specific gravity, 1015; albumin, trace; sugar, 0; granular casts; oxalates.

February 8*th.* Specific gravity, 1020, acid; albumin, 0; several hyaline casts.

25*th.* Specific gravity, 1020; albumin, 0; an occasional hyaline cast.

April 15*th.* Specific gravity, 1015; albumin, trace; oxalates. There were no unusual urinary symptoms; the amount varied from time to time.


Days
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
106°
105°
104°
103°
102°
101°
100°
99°
Normal

The Fever. During October and November there were several paroxysms of fever. From December 1st until the patient's death in May the temperature was carefully recorded. From the first-named date until March 5th there were five periods of apyuria, lasting ten, ten, six, fifteen, and eight days respectively, each followed by a period of twelve, nine, eight, eight, and eight days respectively.

During the apyretic periods the temperature would range from 97° to 98.5°. After a paroxysm of fever the temperature would be subnormal for twenty-four or forty-eight hours. The onset of the periods of fever was somewhat abrupt; the acme of the range would be marked in twenty-four hours. In the earlier paroxysms the temperature was higher than the later. It would rise to 103°, and, with the difference of a degree or a degree and a half between morning and evening, would remain during the paroxysm at this height, falling somewhat abruptly to or below normal in about eighteen hours. In two of the paroxysms there was a crisis and a pseudocrisis. The fever would be preceded by pain in the groin; it would be attended by extreme anorexia and insomnia. The degree of each of these symptoms was remarkable. There was no change in the size of the spleen. The urine would be scanty and loaded with urates. The pulse would range from 65 to 75 during the apyretic period; from 80 to 90 during the febrile period. The respirations were 22 to 26 in the former; 28 to 35 in the latter period. After March 5th the fever became mildly continuous, rising to 101°–102° in the evenings. (See chart for record of a paroxysm.)

Symptoms of cerebrospinal meningitis of tuberculous origin arose two weeks before death. The final invasion of the tuberculous process was seated in the nervous system.

CONCLUSIONS. Hodgkin's disease is in all probability a lymphatic tuberculosis. Fever, recurrent in type, occurs commonly in this infection of the glandular structures. So-called recurrent fever is a symptom, not a disease. In a few rare instances the clinical diagnosis, where such fever prevailed, was malignant lymphoma (Pel), sarcoma (Volckers), myelosarcoma (Hammer), and lymphosarcoma (Remus and Witthower, Seebohn). It must be remembered such distinguished authorities as Ehrlich and Lazarus believe that Hodgkin's disease is a lymphosarcoma, and that the tuberculous process is accidental. Sternberg, on the other hand, has pointed out the differences, and strongly insists upon the tuberculous as *the* process giving rise to the adenitis of Hodgkin's disease. He believes the symptoms are different from other forms of tuberculosis, the anatomy of the gland having much to do with the process. We agree with the conclusions of Sternberg.

SOME OBSERVATIONS IN TWO CASES OF DIVERTICULUM OF THE ESOPHAGUS.

By FRANZ PFAFF, M.D,
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DILATATIONS of the esophagus are comparatively rare. The literature on this subject is not at all voluminous. Besides the different single observations published by the different authors, there are only two larger essays upon this subject, the older one by Zenker and Ziemsen,[1] and the most recent one by Hugo Stark.[2] In Stark's publication the literature on this subject is treated exhaustively. In it all the older cases are tabulated and some original observations added. Since Stark's publication a few new observations have been made by Westphalen,[3] F. Yung,[4] and Schwalbe.[5] Of idiopathic dilatations Dr. Yung cites forty-eight cases, including his own two observations. A few more cases have been published, but the small number shows the scarcity of the material observed. A few new observations may, therefore, be of interest, especially as the result of treatment in these two cases gave a very good, although palliative, result.

CASE I.—I am indebted to Dr. G. M. Garland, of Boston, with whom I saw the patient in December, 1896. At that time the patient was twenty-seven years old. Up to a year before that he was perfectly well. The family history was absolutely negative. So far as the patient and his mother remember, he never had a day of sickness in his life, and never spent twenty-four hours in bed. He even never suffered from the ordinary children's diseases, like measles, etc. The patient complained of some dull sensation at the pit of the stomach, which occasionally amounted to rawness and actual pain, regurgitation of food, and loss of flesh. His weight was 140 pounds. One of the prominent symptoms was a very distressing hiccough. The patient complained that soon after eating, and even during meals, he brought up food by regurgitation. As a rule he spit the food out; occasionally he swallowed it again. The regurgitation of food lasted, however, hours after meals.

The physical examination of the patient was entirely negative. Examination showed that a good-sized stomach-tube passed comparatively easy into the stomach. A slight resistance was felt near the entrance into this organ, which, however, could be overcome by manipulation without using any force. The stomach, after twelve hours' fasting, contained free HCl, some lactic acid, partly digested food, and besides this undigested food, such as meat and other articles of diet, which the patient had taken the day previous. The stomach was washed out thoroughly and Ewald's test breakfast given. After an hour the tube was passed again into the stomach, and again a slight resistance was felt near the cardiac orifice, which, however, could be overcome without using any force, and simply by manipulation. The patient expressed the remainder of his test breakfast. The qualitative and quantitive examination of the same gave normal results. In both these examinations made at one and the same sitting no food came through the tube before it had reached the stomach. A diagnosis was not made at that time. Spasm of the cardia or the esophagus was thought of. As to the food found in the empty stomach, the conclusion arrived at at this time was that this food must have lodged the whole night above the entrance into the stomach—*i. e.*, in the esophagus—and had reached the stomach at the time the stomach-tube was passed into this organ, or shortly before. The patient was seen only the one morning.

At the same sitting he was taught to use the stomach-tube himself. He was advised to take for the next few weeks only liquid food, such as milk, raw eggs, gruels, etc., through the tube, and not to masticate or to swallow any food. He was given a prescription containing bromides and asked to report again in a few weeks.

By some misunderstanding he did not report until October, 1899. He looked in perfect health. He had gained twenty-five pounds, his weight being now 165 pounds. The patient said he had to use the stomach-tube all the time to feed himself (two years and ten months), as food taken the ordinary way was always regurgitated, whereas food taken with the aid of the stomach-tube remained in the stomach. He had noticed that when he swallowed food, and later fed himself with the tube, this food remained in the stomach, whereas that taken before in a natural way came up invariably. Of course, this symptom alone suggested at once the existence of a diverticulum of the esophagus. During the thirty-four months the patient had attempted nearly every day to eat some food by the mouth, being obliged to take his meals with his associates. He was over-sensitive and did not want to let his friends know his trouble, so he sat down to meals daily and "went through the performance of eating." He ate small quantities until the pressure on the pit of the stomach was so great that he had to stop eating or to regurgitate the food, and so get rid of a part of it, before he was able to take new food by the mouth. If he gave up feeding himself by the tube he lost flesh rapidly. The regurgitation of food was never preceded or accompanied by nausea. Sometimes the patient regurgitated food which he had

taken days before. Of subjective symptoms the patient complained still of rawness at the pit of the stomach. If the patient avoided eating by the mouth and could feed himself only by the stomach-tube, he felt better. The soreness and distress at the pit of the stomach disappeared, there remaining only the sensation of dulness. The patient said that, as a rule, he had had no difficulty in introducing the tube into his stomach. By changing his position and by manipulation, without any use of force, he could get the tube easily into his stomach. Occasionally, however, he did have difficulty in introducing the tube. In such instances food would come up first through the tube (the contents of the diverticulum), and when the tube was passed further on he could introduce food through the tube into the stomach. Once or twice every year, however, it would be impossible for him to use the tube. When he had a so-called "bilious attack" the attempt to introduce the stomach-tube was always followed by nausea and vomiting of green bile mixed with mucus, and he was not able to pass the tube into the stomach. These attacks were, however, quite distinct from his ordinary regurgitation. The matter brought up looked different. Only in the beginning did he vomit food; later only bile and mucus. If he abstained from eating or feeding himself for one or two days these attacks would pass off, and any new attempt at eating by the ordinary way would be followed by regurgitation of "sweet food" without bile and without nausea.

As already said, these observations made by the patient himself suggested the existence of a diverticulum of the esophagus. The patient was again examined with an empty stomach. Before the tube reached the stomach 150 c.c. of a mixture of fluid, mucus, and solid contents came up. The contents reacted acid to blue litmus paper, gave no reaction with Congo paper or Guenzburg's reagent. It contained lactic acid, and gave a very marked test for sugar. Before passing the tube further the cavity from which the contents came was washed thoroughly with water. As soon as no particles of food were present in the wash-water the tube was passed further and the patient asked to express. A small quantity of food was expressed, which showed, according to macroscopic and microscopic examination, the same articles of food as the contents which were obtained by introducing the tube into the esophagus. The chemical analysis gave the same results also, showing absence of HCl, etc., so that the question whether the second quantity of food came from a second and distinct cavity could not be settled at this examination. (Three years ago the contents received from the empty stomach showed the presence of HCl, whereas at this examination HCl was absent.) A few days later, November 21, 1899, a new examination was made. The patient had tried to eat an ordinary dinner, consisting of turkey, bread, butter, cheese, and milk, at 6.30 P.M. At 7 P.M. he vomited, as he said, about three-quarters of his dinner, but without nausea. The following morning, as soon as the tube was introduced into the esophagus, but not far enough for it to have reached the stomach, 80 c.c. were expressed through the tube. The contents showed an ordinary reaction of food only partially

digested by saliva. As soon as the 80 c.c. of food were directly expressed the tube was not changed, but wash-water poured in and siphoned out until no solid particles were to be seen in the wash-water. The patient himself introduced the tube now about 10 cm. further and tried to express. Nothing came up directly. Water was poured into the tube and siphoned out, but no solid particles came with the wash-water. An analysis of the stomach contents could, therefore, not be made, none being present. That we had to deal, however, with two distinct cavities was more than probable. In washing out the first cavity the patient complained of pressure pains as soon as 200 or 250 c.c. were poured in, whereas in the supposed second and lower cavity 1000 or more c.c. could be introduced without any pressure pains being complained of.

On the next morning, however, conclusive chemical proof could be obtained that we had to deal with two distinct cavities, in which two different digestive ferments were secreted.

The patient was advised to wash his esophagus and stomach separately until all the wash-water came out clear, then to take Ewald's test breakfast through the tube, using pulverized toast for bread. As soon as he had introduced into the stomach the toast and water the patient ate by mouth some bread and water directly. An hour later, after the patient had finished these two meals, the tube was introduced into the esophagus and 155 c.c. were obtained by expression. The cavity from which the 155 c.c. of solid and liquid material came out was washed until the wash-water came perfectly clear. The tube was now introduced further, and 80 c.c. of colorless, clear fluid containing a few shreds were thus obtained. The analysis of these two contents gave the following results:

Specimen A.	Specimen B.
From upper cavity. Mixture of solid and liquid contents. Filtrate clear yellowish.	From lower cavity. Colorless liquid. Perfectly clear, except for a few shreds.
Blue litmus: red.	Red.
Red litmus: no.	No.
Congo, phloroglucin, methyl violet: negative.	Strong positive.
Albumin: trace.	Good trace.
Fehling's test: strong positive.	Absent.
Results of digestive experiments:	
Coagulated egg albumin + 0.2 per cent. HCl + filtrate: negative.	Totally digested in half an hour.
Egg albumin + filtrate: no action.	Partial digestion.
Starch + filtrate: good action.	No action.

As the patient had had difficulty in bringing Ewald's test breakfast through the tube into the stomach in the above experiment, on account of the tube becoming plugged, and as he was only able to pass scarcely half the quantity

through, I therefore directed him to prepare a combination test of oatmeal and water (two ounces of oatmeal and ten to twelve ounces of water), to be taken into the stomach through the tube, and bread and water to be taken afterward by the mouth. This combination test breakfast we have repeatedly tried in the last year and a half, and always with the same results. From the esophagus a mixture of bread and water came up, expressed after an hour, varying in amount from 60 to 90 c.c., and containing between 4 and 6 per cent. of sugar, lactic acid, ptyalin, but no HCl or pepsin, etc. Then the esophagus was thoroughly washed out and the tube introduced into the stomach. The patient expresses, after such a combination breakfast, from 40 to 90 c.c. of stomach contents, containing pepsin and HCl, the latter varying in quantity from 0.1 to 0.2 per cent.

As soon as the condition was recognized as a diverticulum of the lower end of the esophagus the patient was advised to abstain entirely from eating, but to feed himself only through the stomach-tube. During the past twenty months he has been directed to take per day about 2000 to 2400 c.c. of milk, 500 c.c. of thick soup mixed with different gruels, thick cream, chocolate, about 80 to 100 grams of sugar, salt, Bass' ale, and whiskey. After each feeding he was advised to wash his esophagus out thoroughly, and to do so even oftener in case he should have any dull feelings or rawness in the pit of his stomach. This rawness in the pit of the stomach was due to a local inflammation, as wash-water from the empty esophagus contained at this time very large quantities of squamous cells and leucocytes, indicating some inflammatory process. So long as the patient follows these instructions he feels perfectly well. Even the soreness and distress which he complained of in former times has disappeared completely.

These symptoms recur as soon as he eats by the mouth, which he occasionally does when forced to by circumstances. He eats then by the ordinary way until pressure symptoms set in and he has to regurgitate his food. On such occasions hiccough again makes its appearance, but as soon as he is able to wash his esophagus clean the hiccough and the other subjective symptoms disappear. As a rule, the patient has no difficulty in introducing the stomach-tube into the stomach, provided the esophagas is empty. Occasionally he has to remove the accumulated saliva from the esophagus with water, lest he is not able to introduce the tube into the stomach.

Since prescribing for the patient a regular amount of food per day he has gained fifteen pounds in two months; his weight during the past year has been between 178 and 183 pounds, instead of 140 pounds, as when first seen.

The volume of the diverticulum has not increased materially in the last year and a half. As soon as 220 to 250 c.c. of water are poured into the esophagus the patient complains of pressure pains in the pit of the stomach. That is the same volume of liquid which the patient could bear about two years ago. The diverticulum has apparently not increased in size, but in spite of avoiding as much as possible any distention by food or accumulated saliva the sac does not decrease in size, or at least the passage of food into

the stomach is not made easier. At present his condition seems to be stationary.

During the last two years the tube always meets, at about 51 to 53 cm. from the incisor teeth, a resistance which cannot be overcome by force. But as soon as the patient feels this resistance he draws the tube for about 10 or 15 cm., throws his head backward, and can, as a rule, then pass the tube easily into the stomach without the use of the slightest force. On the way to the stomach there is never the sensation of passing any narrow passage or stricture.

We tried to make some X-ray observations and to take a skiagraph of the diverticulum. I am very much indebted to Mr. Walter Dodd, of the Massachusetts General Hospital, who very kindly made all the X-ray observations. My intention was to pass into the empty stomach one of Kuhn's "spiral-gummi" bougies in order to have a metal sound going from the mouth into the stomach, and as soon as this was in position to fill the diverticulum with bismuth emulsion through a second tube passed into the esophagus. The introduction of the spiral bougie into the stomach and the suspension of bismuth into the esophagus were easily accomplished. The patient himself showed the utmost patience in these experiments. In spite of all care, the pictures obtained were not very satisfactory. On the negative plate one sees the metal sound going further down than the shadow corresponding to the filled diverticulum. The outlines, however, are not very distinct. In other attempts we filled the diverticulum only with bismuth suspension without passing the metal bougie into the stomach. The negatives[1] were much better and showed clearly the position of the diverticulum.

We made a few further tests to test the absorbing power of the esophagus.* In the different hand-books of physiology we still find the statement that the esophagus is capable of absorption. S. J. Meltzer's patient,[6] however, did not feel any effects from alcohol as long as she kept the alcoholic solution in the esophagus. But very small quantities of alcohol poured into the stomach caused the characteristic effects. The same patient, when given atropin into the esophagus, showed no action of this drug, even when it remained there for hours. But a few minutes after the atropin solution has reached the stomach the characteristic action of atropin was plainly visible and felt by the patient.

* The picture of it was shown at the meeting.

Joseph Maybaum[7] proved that potassium iodide or alcohol was not absorbed from the esophagus. Flaum and Pechkranz[8] seem to have obtained similar results. With our patient we made a few quantitative tests with solutions of lactose and sodium chlorid. They proved that no absorption takes place from the esophagus. In each experiment a solution containing the drug remained thirty minutes in the esophagus. It was introduced directly with the aid of a tube, the tube removed and washed, and in this wash-water the quantity of the drug determined which did not remain in the esophagus. After thirty minutes the tube was again introduced, the patient expressed the contents, and the esophagus was then washed repeatedly with water. These wash-waters were added to the quantity obtained by expression.

Experiment I.

Introduced into the esophagus through tube 100 c.c. of water containing 17.2 lactose	17.2 g.	lactose.
Recovered in the wash-water, and which, therefore, failed to enter the esophagus	2.23	"
Actually introduced into esophagus	14.97	"
After thirty minutes 112 c.c. expressed from esophagus; to these were added the wash-water, making together 1225 c.c.		
5.3 c.c. of this mixture contained 0.067 g. lactose, or 1.26 per cent; 1225 c.c. contained, therefore	15.43	"
	+ 0.46	"

Experiment II.

In the experiments with sodium chlorid solution the patient was asked not to swallow the saliva, but to keep his mouth open and to collect the saliva in a porcelain dish. The sodium chlorid solution was introduced into his esophagus and remained there for half an hour. The mode of procedure was the same as in the experiments with lactose.

Saliva during thirty minutes = 28 c.c., containing 0.046 g. NaCl = 0.17 per cent.		
Injected into esophagus 100 c.c. NaCl solution, containing 2.438 g. NaCl	2.438 g.	NaCl
Recovered in wash-water	0.503	"
Actually in esophagus	1.935	"
After thirty minutes recovered from esophagus	1.096	"
	+ 0.021	

Experiment III.

Saliva during 30 minutes = 29.5 c.c. = 0.042 g. NaCl = 0.14 per cent. (little saliva was lost).

Injected into esophagus 100 c. c. NaCl solution containing .	2.438	g. NaCl
Recovered in wash-water	0.5448	"
Actually in esophagus	1.8932	"
After thirty minutes recovered from esophagus . . .	1.8450	"
	— 0.0482	

From these experiments no absorptive power of the esophagus can be deduced. The esophagus seems to have no more absorptive power than normal skin.

CASE II.—I am indebted to Dr. Tierney, of Leominster, Mass., for this case. I saw the patient the first time July 8, 1900. He was sixty-nine years old. In this, like Case I., no etiologic factor could be found in the history for the formation of a diverticulum. The examination of this patient also proved negative. No tuberculosis, syphilis, etc. The patient said that the act of swallowing became more and more difficult for six years past. He had to give up first solid food, and later the swallowing of liquid food became more and more difficult. All the food "went up and down in the esophagus, and he could not swallow the same." Even milk, after remaining there for quite a while, was regurgitated, not curdled. The patient had lost constantly in weight in six years—in the last two years alone thirty-eight pounds, and in the last few weeks rapidly more. He suffered intensely. He saw food before him, but could not eat it. He saw water, and could not drink it. But he never had any pain. The patient, a comparatively tall man, weighed in a heavy suit ninety-seven pounds. He looked the picture of starvation. At first sight one was inclined to think of a carcinoma of the esophagus, but later developments proved the case to be one of a diverticulum situated near the bifurcation of the bronchi.

The case as such does not offer any unusual features of interest, and I relate it only on account of the improvement in the patient's condition which followed as soon as we were able to pass a sound beyond the diverticulum and feed the patient regularly. At first the introduction of stomach-tubes, sounds catheters, bougies, etc., seemed to be impossible. For eight days all kinds of devices were tried three times a day, each sitting lasting from one to two hours. I am very much indebted to Dr. Elliott P. Joslin for his unvarying assistance and help in this case. The patient and his doctors were often quite exhausted after such trials, but the doctors went home after an unsuccessful attempt to pass the diverticulum, whereas the poor patient was left to starve.

But our attempts and the patient's patience were not in vain. At first we were occasionally able to pass the catheter beyond the diverticulum and a stiff stomach-tube even into the stomach, and so to feed the patient by the

mouth. Of course, rectal feeding was resorted to at the same time. Afterward the patient learned very soon to pass a moderately stiff catheter beyond the diverticulum, and so was able to feed himself regularly. He now takes daily three meals, each one less than one liter capacity, not feeling the necessity for more food. The patient has gained twenty-five pounds in six months, and feels perfectly well and content and able to do his work.

He has attempted repeatedly to eat by the mouth, but without result. The diverticulum fills up, and he cannot swallow any food. Attempts to introduce more food are followed by regurgitation. Like the patient in Case I., he can empty the diverticulum and the esophagus by simply bending his body, when the contents flow out easily by straining slightly.

When I saw the patient last, on February 21, 1901, he demonstrated to me how easily he could pass the tube beyond the diverticulum. In less than half a minute he had his long catheter half-way into the esophagus in the right position and ready to pour liquid food into the attached funnel. He compared his performance with our first attempts at the same, and a happy smile went over his face.

Both cases have this in common, that there was no improvement after the passage of larger tubes and the continued feeding through these tubes. In some other cases the authors observed after such treatment at least temporary improvement. Both patients are kept in good physical condition by feeding through the tube. In Case I. the absence of saliva from the stomach does not as yet have any bad influence upon the amount of HCl secreted.

The diverticulum in Case II. could be operated upon. A method of operation for a diverticulum situated as it is in Case I. has as yet not been advanced.

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2. Die Divertikel der Speiserochre von Hugo Stark, 1900.
3. Archiv für Verdauungs Krankheiten, v. p. 106.
4. Ibid., vi. p. 45.
5. E. Schwalbe. Münchener med. Wochenschrift, 1899, p. 44.
6. Berliner klin. Wochenschrift, 1888, iv. p. 8.
7. Arch f. Verd. Krht., 1896, i. p. 388.
8. Gazeta lekarska, v. p 24.

DISCUSSION.

DR. MELTZER: I wish to say, in the first place, that the absorption within the normal esophagus is, indeed, very low, but it is still better than in the normal stomach. The exact proportions I have given in a paper on the absorption of strychnin from the alimentary tract. In an abnormal esophagus, however, as in the interesting case reported by Dr. Pfaff, no absorption whatever takes place. I demonstrated it some thirteen years ago in a case of consecutive dilatation of the esophagus, where atropin, alcohol, etc., exerted no influence whatsoever as long as they remained within the esophagus.

In the case of Dr. Pfaff there was at first a diagnostic question between tonic contraction of the cardia and diverticulum. Many years ago I called attention to a diagnostic point which has its value just in such cases as this. In all discussions on stenosis of the esophagus we find the question raised only whether the path is free in the direction toward the stomach; while it is just as important to know whether the passage is free in the direction from the stomach upward. Now, patients with tonic contractions of the cardia can rarely vomit. When they vomit it is from the sac above the cardia, which can easily be established. Such patients again can have no real ructus. They often belch, but auscultation at the ensiform cartilage will soon convince that the gas is not coming from the stomach. Now, these and other points are absent in diverticulum or other valve-like causes for stenosis, etc. I do not wish to take up your time by dwelling any longer on the particulars, but I wish again to call your attention to the value of this diagnostic point.

OSTEITIS DEFORMANS.

By FREDERICK A. PACKARD, M.D., J. DUTTON STEELE, M.D.,

AND

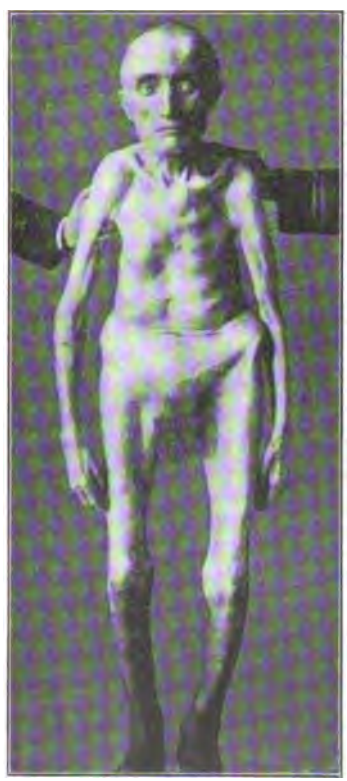
THOMAS S. KIRKBRIDE, Jr., M.D.,
OF PHILADELPHIA.

Before proceeding with the report of this case we would state that the histologic examination of the tissues was begun by the late Dr. T. S. Kirkbride, Jr., whose untimely death from typhoid fever, contracted in laboratory work, came soon after the beginning of what promised to be a brilliant career. The work so begun by Dr. Kirkbride was taken up and carried to completion by Dr. Steele.

In April, 1899, there was admitted to the men's ward of the Philadelphia Hospital a German, aged sixty-two years, who for some months had been an inmate of the almshouse department. Until the onset of an acute indisposition, for which he was referred to the wards, he had attracted no particular attention. Owing to the fact that he could speak almost no English and was very deaf, with some impairment of mental power, nothing could be learned of his past history. Attention was attracted to him by the size of his head, which was that of a man very much larger than he was. Not only was his head large, but it had a peculiar shape, being rather box-shaped, with a marked projection of the forehead, flattened crown, and a distinct tumor at the junction of the left temporal, frontal, and parietal regions. (See Figs. 1, 2, and 3.) The face was somewhat larger than that of a normal individual of the same size, but was small in proportion to the size of the calvarium. The mastoid processes were large and heavy, and the lower jaw was also disproportionately large, but was not prognathous. The soft parts of the face showed nothing out of the way. Measurements of the head were taken shortly after his admission, and again about a year later. For the purpose of comparison both sets of measurements are inserted here:

	Shortly after admission.	February 12, 1900.
Bitemporal	14 cm.	15½ cm.
Binaural	15 "	14½ "
Fronto-occipital	20 "	20¾ "
Occipitomental	20 "	23 "
Biparietal	17 "	19½ "
Angular	13 "	13 "
Greatest circumference	63 "	63 "
Circumference of vault from meatus to meatus	40½ "	41 "

FIG. 1.

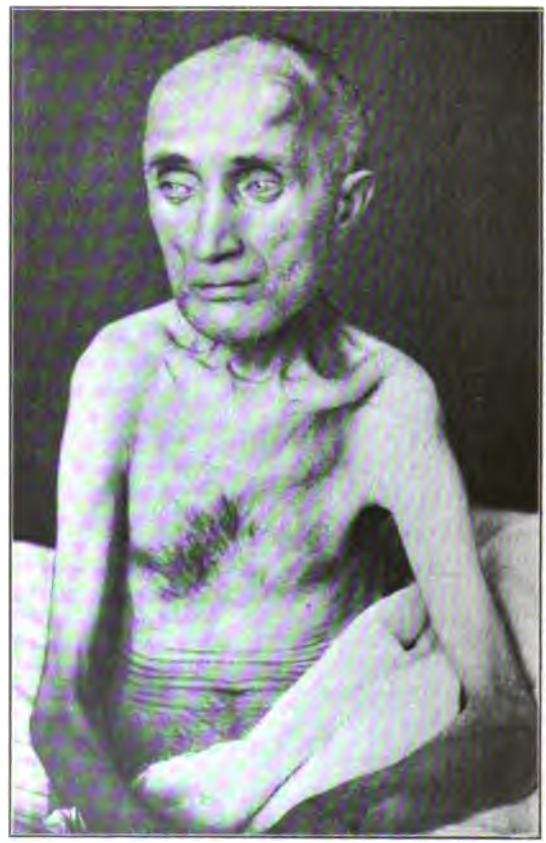


Photograph of subject of report, showing shape of head, frontal tumor, and bony deformities.

The head and face, therefore, were rather egg-shaped, with the larger end of the oval pointing upward, as is well shown in the figures. The tongue was of normal size, the vault of the hard palate capacious, but not deep; the

alveolar processes were excessively thick. All of the sutures and fontanelles were closed, and showed no depression or ridging. The speech was very peculiar and practically unintelligible, although not entirely because of ignorance of the language, as an occasional English word could be discerned so thickly emitted that its recognition was almost impossible. The larynx

FIG. 2.



Photograph of subject of report, showing size of head, frontal tumor, clavicle, and peculiar shape of chest.

was very large and broad, giving the neck a rather full appearance, but the thyroid gland could not be outlined.

A curious alteration of the shoulder girdle was present, due to the fact that, while the clavicles stood out prominently because of thickening of the bones and increase in their natural curves, their direction was almost backward.

The upper ends of both humeri, especially the heads, were much thickened, and the natural curves and elevations were very much exaggerated. On both sides there was marked anterior curvature at the level of the deltoid insertion.

FIG. 3.

Showing especially the separation of the knees when the ankles were in contact.

The elbow-joints appeared to be normal, as were also the bones of the left forearm. In the right forearm there was marked curvature of both bones toward the radial side. On both sides the radius and ulna had a distinctly rough and uneven surface. The appearance of the chest can best be appreciated by a glance at Fig. 2. Above, the chest was small and narrow, with the anteroposterior diameter almost equal to the lateral, while below the chest was large and bulging. No substernal dulness could be detected. The xiphoid process was very prominent and broad, and the ribs were distinctly thick and heavy. On each side the tip of the eleventh rib was almost in contact with the crest of the ilium. The costosternal angle was very oblique. There was marked forward curvature of the spine, with very evident thickening of the lower dorsal and upper lumbar vertebræ. Dorsocervical kyphosis was present without scoliosis. The scapulæ were apparently not enlarged.

Examination of the abdomen showed that there was excessive pigmentation of the skin and growth of hair on the anterior surface. Just beneath the costal margin there was a deep transverse furrow extending across the abdomen. The general outline of the abdomen was that of a diamond, the angles of which were formed by the xiphoid angle, the pubis and the junction of the ribs with the crests of the ilium. The pelvis resembled in shape that of the female rather than that of the male, being very broad and heavy, and the superior basin being very capacious. The distance between the anterior superior spines was 31 cm. The iliac crests were remarkably heavy, and projected far beyond the level of the trochanters. The extreme lateral width of the pelvis was 34 cm., the intertrochanteric distance being 30 cm., while the patient's total length was only 57 cm. The thigh bones were somewhat large, but were not much deformed, except for the condyles, which were very large. The patellæ were about normal in size. In the skin over the left patellar tendon there was a flat circular mass of about 2.5 cm. in diameter, apparently situated in the superficial layers of the skin, and giving to the finger the sensation of an enchondroma. Both tibiæ were greatly increased in thickness, especially on the anterior aspect, the surface of which was rough. This thickening and prominence were more marked on the left side than on the right. The fibula of the left side was decidedly thickened. Both legs showed marked outward bowing, the distance between the knees when the feet were placed together being 7.5 cm. The hands and feet were not enlarged.

In no part of the body was there evidence of any involvement of the soft parts. The whole attitude of the patient on standing up irresistibly reminded one of that of the orang-outang.

On his admission the man had a large pleural effusion in the right side. This was withdrawn, and did not reaccumulate. He, however, remained feeble with progressively increasing emaciation and slow growth of the tumor in the frontal bone until his death, about a year after coming under observation.

Autopsy was held twenty-four hours after death. The following notes were made at the time: Rigor mortis is well marked. External conformation as described in clinical notes. On removing the scalp there is found a large subcutaneous tumor springing from the frontal bone to the left of the median line. The tumor is of soft consistence. In places the scalp is remarkably thin, especially in the left temporal region. The outer surface of the calvarium has a rather bluish appearance, and seems somewhat more vascular than normal. The saw cuts very easily through the bones of the skull. The tumor mentioned above is found to measure 4 x 5 cm. at its base, and has an elevation of 2 cm. The calvarium is fairly uniformly increased in thickness,

FIG. 4.

Calvarium.

measuring from 1¼ to 2 cm. (See Fig. 4) The diploe is apparently absent, excepting in the frontal and occipital regions. A little to the left of the median line at a point corresponding to the superficial tumor the bone is thickened to 3 cm., owing to the presence in the diploe of a soft growth corresponding in consistence to that seen externally. The growth projects through both the inner and outer tables. The brain is adherent to and almost incorporated with the growth. The whole hollow of the frontal bone on the left side is occupied by a large irregularly rounded mass of soft consistence, and measuring 5 cm. in all directions. The base of the skull appears large and gross, and all of its concavities are deepened except the sella turcica, which is of about normal size. The inner table of the calvarium is

deeply grooved for bloodvessels and freely perforated by small foramina. The base of the brain shows great overfulness of the bloodvessels. The membranes of the brain seem unaltered over a greater part of the surface, but over the convexity the pia is slightly opaque. In the left frontal region anteriorly to the operculum the brain substance is torn and softened at a point corresponding to the tumor of the calvarium. On the posterior end of the third frontal convolution there are some small whitish granules (sarcoma or tuberculosis?). Similar masses are found bordering upon the longitudinal sinus of the left side.

On the right side there are some old adhesions of the pleura, especially near the apex; the left pleura contains a small amount of fluid. The layers of the pleura on the left side are much thickened, and there is on them a gelatinous substance which partially fills the cavity. A large "milk patch" is present on the anterior wall of the left ventricle. The heart muscle is soft and flabby, but there is no other alteration of the walls or valves. There is an area of atheroma at the root of the aorta. The left lung is almost but not quite airless. The diaphragm on the left side shows irregular thickenings of yellow color looking like sarcoma. The right lung shows only hypostatic congestion. The spleen is large, measuring 13 x 8 x 3.5 cm. The pulp is very soft and the Malpighian bodies prominent. The left suprarenal capsule is thin, and the distinction between the cortex and the medulla is very poorly marked. The kidneys are large and pale, with somewhat prominent vessels, and capsules stripping off readily. The right suprarenal resembles the left except for the fact that there is a post-mortem cavity in the medulla. The liver shows slight distention of the small bile passages; the substance of the organ appears fairly normal. The bile ducts are patulous, and the mucous membrane of the gall-bladder has a normal appearance. The pancreas is rather small, but seems otherwise normal.

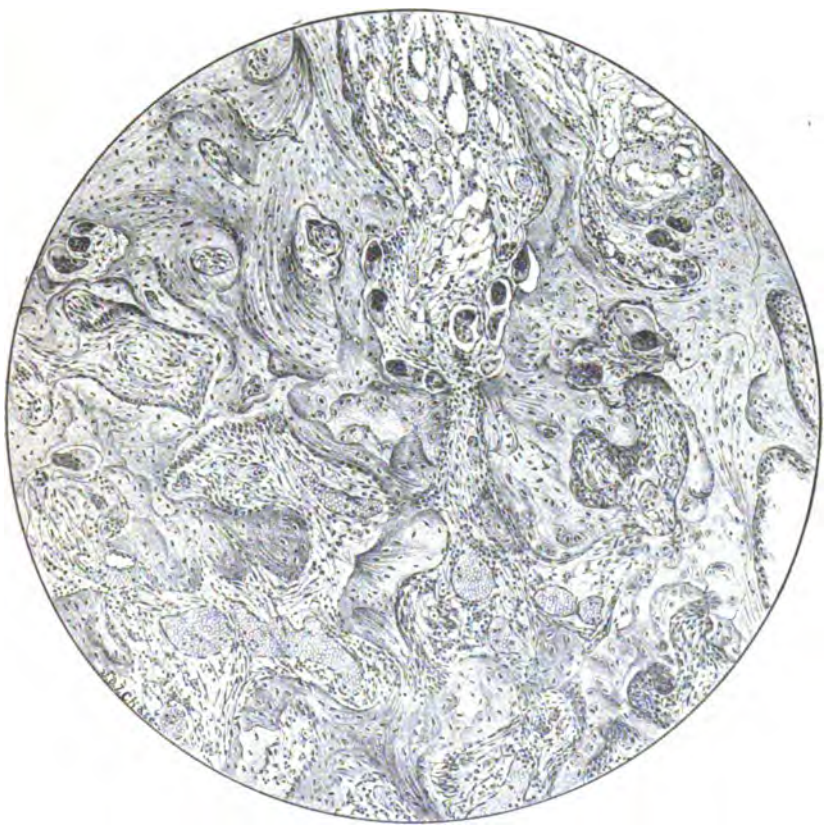
Owing to the limited time allowed for the autopsy, it was impossible to remove the spinal cord or the peripheral nerves. It is much to be regretted that preservation of the thyroid gland was for some reason inadvertently overlooked. Grossly it showed no change, but it would have been advantageous to have proved its condition by microscopic examination. While changes in the spinal cord described by some observers are probably, as they have pointed out, due to the accompanying arteriosclerosis, our inability to remove the spinal cord because of lack of time is a source of regret.

Microscopic Examination.—Clavicle. A portion of the bone was taken from about the middle of the shaft of the thickened portion. It was cut with the saw with somewhat greater ease than a normal bone. Decalcification in 5 per cent. nitric acid and phloroglucin was complete in twelve hours, showing the small amount of lime salts in the tissue, as ordinary bone requires from three to four days for decalcification in this solution.

The sections were stained by hematoxylin and eosin. The part of the shaft that is usually compact bone substance, with regular Haversian systems, consists of a finely porous structure in which areas of unaffected bone

alternate with spaces that are evidently the result of its absorption. These spaces are filled with a fibrous-tissue reticulum. The cells of the spaces are mostly spindle in character; but there are also many round cells, with deeply-staining nuclei, polymorphonuclear leukocytes, and a few nucleated red cells, and some fat cells. Most of the interspaces are exceedingly vas-

FIG. 5.



Section of the shaft of the diseased clavicle. Leitz ocular 3, objective 3. The general asymmetry, absorption spaces and the fibrous, medullary substance, containing giant cells and many bloodvessels, are well shown. There are several areas of uncalcified new bone.

cular. In many there are networks of dilated capillaries whose walls are but a single layer of endothelium. Larger arteries cannot be seen in the sections obtained. (See Fig. 5.)

The reticulated structure runs almost to the periosteum, and a thin shell immediately under it is the only representative of the compact substance.

In the interspaces are numerous groups of giant cells with many nuclei. These cells lie in the edges of the unaffected bone, and are apparently engaged in its absorption.

Running through these interspaces and through the bone itself are masses of closely packed cells, resembling osteoblasts, with a fibrous matrix. This is evidently an attempt at the formation of new bone, but in no place is it calcified. The dividing line between the unabsorbed and new bone is sharp, and there is every indication that the processes are distinct from one another.

Skull. The distinction between the diploe and outer and inner tables is entirely lost, as far as could be seen from the sections of the bone obtained. Tnere is a thin and irregular plate of compact bone under the periosteum, but elsewhere the bone is honeycombed by absorption spaces, giving it a porous structure. These interspaces (as in the clavicle) are filled by a connective-tissue reticulum containing spindle cells, round cells with large nuclei, polynuclear leukocytes, and a few giant cells. This last variety are not as numerous as in the sections from the clavicle. As in the clavicle, there are bundles of osteoblasts in a fibrous matrix running through the bone and spaces in all directions, evidently representing new bone. The interspaces in the skull are not as vascular as in the clavicle; however, they are well supplied with blood by capillaries. No large arteries are seen in the section. Sections from the tumor of the frontal bone show it to be a typical giant-celled sarcoma. The mass of the tissue consists of bundles of spindle cells and masses of round cells, but there are also many larger cells with a single, irregularly staining nucleus, and numerous giant cells with five or more nuclei. In general the sections examined show the following changes:

1. Absorption of the healthy bone.
2. Formation of new bone coincident, but in no way connected, with the absorption process.
3. The failure of calcification in this new bone.
4. The destruction of the regular structure of the bone and the addition of new uncalcified bony tissue.
5. The formation of a giant-celled sarcoma in the affected portion of the skull.

These changes correspond closely to those described by Paget, Stilling, and others who have subjected their cases of osteitis deformans to a microscopic examination.

Suprarenal Bodies. Microscopic examination shows these structures to be normal.

Hypophysis Cerebri. Sections of the hypophysis cerebri show no abnormality.

Nodule from the Pia. Consists of a collection of round and spindle cells with a moderate amount of intercellular substance and with deeply-staining nuclei. It is well supplied with bloodvessels whose walls consist merely of a single layer of endothelium. In many places giant cells are found. The nodule is evidently a metastasis from the tumor of the frontal lobe.

The nodule from the diaphragmatic pleura is of the same structure as the nodule in the pia, and has evidently the same origin. It also shows numerous giant cells.

In the literature we find references to ninety-nine cases reported as osteitis deformans.[1] Careful study of these cases show, however, that four of them were certainly instances of some conditions other than even slightly developed osteitis deformans. Twenty-nine may possibly have been instances of this disease, but the facts given were not sufficiently definite to warrant the statement that they were typical cases of osteitis deformans. Many of these reported as instances of this disease were apparently examples of tumors of bone of more ordinary nature, or of osteomalacia or fragilitas ossium, with local enlargement secondary to fractures. Sixty-six cases were found which, in our judgment, are typical instances of the disease described by Paget, in 1877, in an article in the *Medico-Chirurgical Transactions.*

ETIOLOGY. Among the cases so far reported forty-one (including our own) were males, twenty-four females, and in two the sex is not stated. The youngest patient at the time of coming under observation was that of Watson, whose age was thirty-nine years, while two patients (Silcock's and Lloyd's) were eighty-two years old when they were first seen. Moizard and Bourges have, however, reported a patient who was seventy-three years of age when coming under observation, but the disease seems to have quite definitely started at the age of twenty-one. The average age at the time of coming under observation was sixty-one years; the age at the time of onset was capable of determination in fifty-one cases, and averaged forty-nine and one-half years, the youngest of these being the case just mentioned, the oldest patient at the time of onset being between seventy-nine and eighty years of age. As will be seen, there is a marked difference between the time of coming under observation and the time when the first symptoms of the disease were noted; eleven of the fifty-one cases noted had symptoms definitely pointing to the onset of their disease when they were forty years old or younger. It can, therefore, hardly be said to be exclusively a disease of those very advanced in years.

[1] Since the presentation of this paper a case has been reported by Atkinson (Maryland Medical Journal, July, 1901). The patient was a male, aged thirty-seven years. The bones affected were the skull, left forearm, and both femora, with considerable deformity. There was no autopsy. The case is apparently one of true osteitis deformans.

The mental capacity of our patient was but slight. In one case from the literature (Joncheray's) the patient and one other member of the family suffered from insanity, while a patient of Lunn's was insane. Inheritance seems to play but a small part in the etiology of the disease, although among the cases which we have studied we found two brothers with the disease reported by Lunn, while Pic and Robinson have each reported a case where the disease was present in two members of the same family.

The etiology of osteitis deformans is, therefore, very uncertain. It is undoubtedly a disease of advanced life, although, as we have mentioned, in eleven of the cases collected the disease began before the age of forty, while in the case of Moizard and Bourges the disease began at as early an age as twenty-one years. The influence of heredity is doubtful. In reviewing the literature there seems no striking evidence of any marked influence exerted by consanguineous marriages, nor does there seem to be any marked neurotic tendency in the families of those suffering from this disease. While a large proportion of the cases are found in English journals, too much importance should not be attached to locality as an etiologic factor, as the disease was first described by Paget, and we would expect his countrymen to be more familiar with the disease described by him than those whose attention had not been particularly drawn to the subject. In this connection it is interesting to note how frequently a series of cases are reported in rapid succession in various countries, showing that the mere fact of the public mention of the disease would seem to excite interest in the condition sufficient to cause recognition of other cases.

SYMPTOMATOLOGY. The analysis of the cases reported show that in 14 enlargement of the head was first noted; that in 13 deformity of both tibiæ was mentioned as the first sign of the disease; in 11 the left and in 6 the right tibia was first involved; while deformity of the spine was first seen in 2; of the right radius in 2; of the right clavicle, lower jaw, and sternum each in 1 case.

Analysis of the cases in regard to the bones affected at the time of coming under observation was not possible in all of the cases. In those where sufficient details were given it was found that deformity was distributed as follows: In 49 of the cases the bones of the skull were involved. (It should be noted that among the 66 cases from the literature 9 departed from the type described by Paget, in the fact

that there was no manifest enlargement of the head, 1 of these cases having been seen by Paget and considered by him a true instance of the disease.) Both tibiæ were affected in 47, the right tibia alone in 2 cases, the left tibia alone in 1 case. In 40 cases both femurs were affected, while the right femur was alone involved in 3, the left femur in 1 case. The spine was affected in 31 cases when they came under observation. In 24 cases both clavicles were thickened and deformed, the right clavicle being affected alone in 3 cases, the left in 4 cases. The bones of the pelvis were affected in 21 cases. In marked contrast to the frequency of involvement of the tibiæ, the fibulæ were found to be affected in only 10 cases. The humeri were symmetrically involved in 14 cases, while in 3 cases that of the right side and in 4 that of the left side were involved. Both radii were affected in 11 cases, while in 5 the right alone and in 3 the left radius alone were affected. In 10 cases the ulnæ were involved, the left ulna being deformed in 2, while the right ulna was noted in no case as being affected where the left escaped. The scapulæ were involved in 6 cases. The ribs were thickened in 16, while the sternum was involved in 7. In 8 cases it is mentioned that the lower maxilla was apparently affected by the disease, while in 1 case it is stated that the bones of the face were involved. In only 8 instances were the patellæ affected. The metatarsal bones were involved in 5, the tarsal bones in 2 cases, and the calcaneus in 1 case. It is seen, therefore, that after the skull the tibiæ are the bones most frequently affected, these being followed by the femurs, spine, pelvis, and clavicles, ribs, radii, and ulnæ. This distribution would seem to rather point toward the fact that pressure and gravity had at least a large share in the production of the deformities.

While in many of the cases there has been complaint of pain in the bones subsequently affected, our study of the literature would not cause us to attach much importance to this as a symptom of the disease, nor, in fact, has the latter much symptomatology, the results being almost entirely objective.

So characteristic is the deformity in well-marked cases that it has seemed well for us to reproduce here Paget's original illustrations, with a few others from the literature. (See Figs. 6, 7, 8, 9, 10, and 11.) We would draw particular attention to the diminution in height, the curious deformity of the shape of the chest, the forward bowing

of the head, the lozenge-shaped abdomen, the transverse sulcus running across the abdomen, the broadening of the pelvis, and the outward curvation of the lower extremities. To all these points attention has been drawn by previous writers. They make up a clinical picture which should not escape observation.

The relative frequency of malignant growths which was first pointed out by Paget in his original communication, and which has been frequently mentioned by later writers as characteristic of the disease,

FIG. 6.

FIG. 7.

Fig. 6.—From Paget's original paper. (Medico-Chirurgical Transactions, 1877.)
Fig. 7.—From Paget's original paper. Ibid.

would hardly seem borne out by a review of cases in the literature. Among them we find that 1 case (Clutton's) had a history of cancer in the family. Out of 66 cases, 3 had cancer. Including our own case, making a total of 67 cases, 5 had sarcoma; 2 cases had tumors of non-malignant nature. In 1 case (Lyon's) there was combined osteitis deformans and arthritis. From these facts it would seem that possibly too much stress has been laid on this association in the accounts found in the text-books. When we bear in mind that this

disease is especially prone to affect those beyond middle age, it is not surprising that about 4.5 per cent. of the cases had cancer, although the high percentage of 7.5 per cent. of sarcoma must have some significance.

DIAGNOSIS. The chief difficulty in the matter of diagnosis is the determination as to whether a given case of deformity involving but

FIG. 8.

FIG. 9.

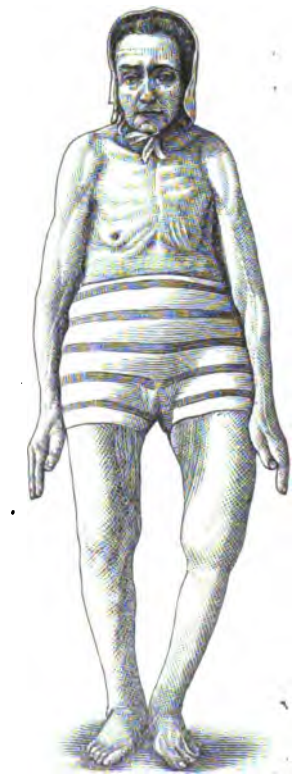


Fig. 8.—From Paget's original paper. (Medico-Chirurgical Transactions, 1877.)
Fig. 9.—Marie's case. (Nouvelle Iconographie de la Salpêtrière, 1894.)

one long bone is an incomplete case of osteitis deformans or whether it should be considered as a purely local affection. In some of the cases in the literature this question cannot be decided. The simultaneous involvement of more than one bone, particularly if the two bones be far removed from each other, and therefore not affected by

a possible local cause, should make us suspicious of osteitis deformans, providing no manifest cause, such as syphilis or malignant growth, could be assigned. The differential diagnosis of this disease from others which apparently are somewhat closely allied to it, in being so far as

FIG. 10.

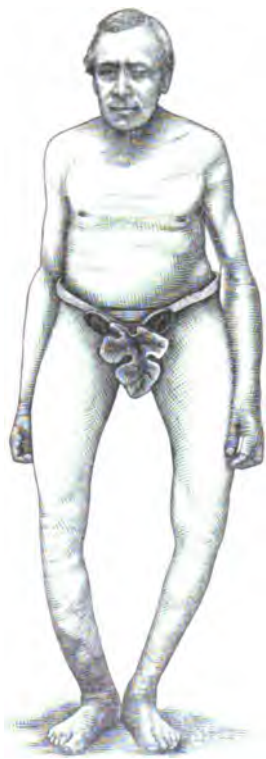


FIG. 11.

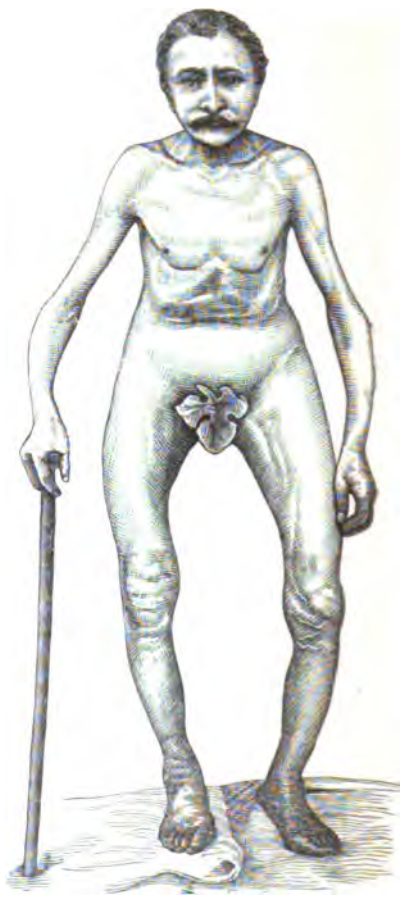


Fig. 10.—A. Robin's case. (Nouvelle Iconographie de la Salpêtrière, 1894.)
Fig. 11.—Gombault's case. Ibid.

we can at present see disorders of the growth of the skeleton, should not be a matter of difficulty. In mollities ossium, to which disease this seems certainly to bear some relation, there is not the same thickening of the bones as is seen in this disease, nor is the head involved.

In fragilitas ossium we have deformity produced by the fractures which have taken place, but, except for the thickening around these fractures, there is no hypertrophy of bone. Acromegaly shows but few features in common with this disease, while it differs from it in the shape of the head, in the seat of the deformity, and in the character of the latter. In osteitis deformans the cranium is triangular, with the base upward; in acromegaly the base is below, from the fact that in the former disease the calvarium is chiefly involved, while in the latter disease the lower jaw and orbital arches are involved far more than is the calvarium. From leontiasis ossium this disease differs in the fact that the bones of the face are not affected, or only slightly, in osteitis deformans, while in hyperostosis cranii the long bones escape. To giantism this disease has not even superficial resemblance; in fact, the patient's stature is diminished owing to the bending of the long bones and to the almost constant dorsocervical kyphosis.

TREATMENT. Occasionally in the literature the statement is found that the pains accompanying the development of this disease seemed to be relieved by the use of iodide of potassium. In a far greater number of cases, however, the use of this drug has been productive of no relief, and, so far as we could find, there was no evidence of its producing any diminution of the size of the bones in cases which are evidently osteitis deformans and not simply osteitis due to syphilitic infection.

PATHOLOGY. The characteristic features of the morbid anatomy of osteitis deformans can be summarized as follows:

Skull. The distinction between the outer and inner table and the diploe is entirely lost. The entire thickness of the cranium is composed of finely porous bone substance, bounded on the inner and outer surfaces with a thin plate of harder bone. Microscopically the porous substance is seen to consist of a network of thin bony processes. The canals of the Haversian systems are enlarged and confluent, evidently the result of absorption. In the lacunæ, representing the normal medullary substance, are numerous giant cells, leukocytes, and fat cells, contained in a network of vascular connective tissue. Running through the affected areas, and seen as well in the healthy portions of the skull, when such are present, are bands of new-formed bony tissue. The osteoblasts of this new bone, while present in con-

siderable numbers, are not as plentiful as in healthy growing bone, and are irregularly arranged. The branching processes of the new canals are shorter than normal or are entirely lacking. The important characteristics of this attempt at regeneration is that the new substance remains uncalcified, and is in time reabsorbed. The border line between the new and old bone is sharply defined, indicating that the two processes are in no way connected. Most observers state that the regenerative process originates in the periosteum, or from the dura, while von Recklinghausen holds that it comes from the medulla. In our own sections the new tissue appears to come from the periosteum.

The result of the combination of these absorptive and regenerative processes is a total destruction of all symmetry in the internal structure of the skull or long bones.

As a rule, the presence of the uncalcified new bone substance renders the cranium softer than usual, but in some places areas of sclerotic bone tissue of ivory-like hardness are found.

In the long bones the normal relation of compact and cancellated structure is entirely destroyed. The outer walls of hard bone are represented by thin, irregular plates lying directly under the periosteum. In general, the histologic picture here is the same as that of the skull, except that the medullary substance is more fatty, and that certain changes are observed that von Recklinghausen classes as retrogressive and progressive. The result of the former is the production of cysts filled with gelatinous substance. The progressive changes produce fibrous tumors or giant-celled sarcomata. The latter are sometimes found in the skull, as in the case here reported, but are rare in this position.

In the bodies of the vertebræ the histologic changes are practically the same as in the skull.

A consideration of the morbid anatomy of the various bony structures affected in osteitis deformans readily explains the clinical features of the condition. The thickening of the cranium and of the long bones is due to the formation of asymmetrical new bone tissue. In the long bones and the vertebræ the fact that this new tissue remains uncalcified and that the compact substance is being continually absorbed causes weakening, and the bending that results is the characteristic deformity of the disease. The tendency to fracture,

seen in osteomalacia, is absent in osteitis deformans, since the presence of uncalcified new bone has a tendency to make the bones elastic and not easily broken.

ETIOLOGY. Up to the present time there is no thoroughly satisfactory explanation of the conditions necessary to produce the lesions of osteitis deformans. However, it may be of interest to briefly review the various theories that have been advanced. Von Recklinghausen holds that the process of absorption is a true osteomalacia associated with inflammatory processes, which commences synchronously with the destruction of the bony tissue, and leads to the transformation of the medullary substance into fibrous tissue. From this the processes of new bone grow out. The exciting cause, in his opinion, is mechanical. He bases his theory on the following facts:

1. That the cysts and sarcomata in the medulla, which he considers to be the first manifestation of the disease, occur at those points where the skeleton is most exposed to violence.

2. That the thickening occurs at the points of greatest strain—that is, in the shafts of the long bones and in the vertebræ.

3. That the skull is often affected, because it is exposed to extremes of heat and cold to a greater extent than is the rest of the body. These conditions act largely through their effect in producing contraction in the bloodvessels.

Paget thought that the whole process was inflammatory, associated with absorption, and explains the occurrence of the connective tissue in the medulla as a result of inflammatory hyperplasia.

Stilling thinks that the absorptive process is the result of a rarefying osteitis with its usual accompaniment, the formation of new bone, which, however, remains uncalcified.

Lancereaux has advanced the theory that the new bone formation is an attempt at reinforcement of the long bones which have been weakened by absorption. This view is rendered untenable by the fact that the new tissue is formed not upon the concavity, but upon the convexity of the deformed shafts.

None of the last three authorities advances any theories as to the immediate cause of the disease. The theory that the exciting cause is mechanical renders it necessary to assume some predisposing condition, and up to the present time no satisfactory explanation has been advanced. It has been asserted by some that the process is a

trophic one, associated with lesions in the nervous system. Stilling found a periependemal sclerosis in one of his cases. Von Recklinghausen describes masses of round cells around the bloodvessels of the cord in one instance. Gilles de la Tourette and Marinesco, and Levi demonstrated sclerosis of the posterior and lateral columns and much degeneration of the bloodvessels of the cord. However, the absence of all clinical evidence of trouble in the nervous system and the results of many examinations that have shown the cord and bone nerves (von Recklinghausen) to be perfectly normal render it unlikely that the lesions referred to have anything to do with the origin of the condition.

DIAGNOSIS. The diagnosis between osteitis deformans and other affections of the skeleton of somewhat similar character is not difficult when based upon a study of the distribution of the lesions and their pathologic histology. The disease most closely allied is osteomalacia; indeed, the two affections merge into one another. The main point of difference is that in osteitis deformans synchronously with the absorptive process a process of regeneration takes place. The callus that forms about the fractures that are so common in osteomalacia somewhat resembles the new bone of osteitis deformans, except that it is localized about the seat of a fracture. It often shows a lack of calcification. Moreover, fractures do not occur in osteitis deformans. The absorptive processes of both diseases are practically identical in their origin and appearance.

Leontiasis ossea affects the bones of the face, and the histologic picture is that of osteosclerosis. The same may be said of hyperostosis cranii and gigantism.

Several writers upon the subject, especially Lancereaux and Richard, have made an effort to show that arthritis deformans and osteitis deformans were different manifestations of the same disease. They claim that both originate in some trophic disturbance, and in one the joints, in the other the shafts of the long bones and the skull are affected. Their evidence has been entirely clinical, and consists of several cases in which the two diseases appeared to be coexistent. No autopsy upon an undoubted case of osteitis deformans has borne out their theory.

Our conclusions from the study of this case and of the literature of osteitis deformans would be as follows:

A. From the Clinical Stand-point.

1. Beside our own case 66 true cases of osteitis deformans are found in the literature.

2. Osteitis deformans is a distinct disease of obscure etiology, but possibly allied to although not identical with osteomalacia, fragilitas ossium, and acromegaly.

3. The disease is one especially of later adult life, although its onset has been noted at as early a period as the twenty-first year. Of the 67 cases, 61 per cent. occurred in males, 35 per cent. in females. In a small number of cases trauma has seemed to play a part in the etiology. There is very little evidence of a family tendency to the disease, although there are a few examples in the literature.

4. The subjects of the disease bear a striking resemblance to each other in their general characteristics, the most noteworthy features of which are enlargement and forward projection of the head, dorso-cervical kyphosis, the prominence of the clavicles, the spreading of the base of the thorax, the diamond-shaped abdomen crossed by a deep sulcus, the relative increase in the width of the hips, and the outward and forward bowing of the legs.

5. The bones most frequently affected are those of the cranium, the tibiæ, and the femurs, in the two former of which the deformity was usually first noted. There is a curious preponderance of cases wherein the left side was either first or most involved, although at times it was noted that the enlargement was crossed, so that the lower extremities of one side while the upper extremities of the other were involved to the greatest degree.

6. The association with malignant disease, while present in our case, would seem to be not quite so frequent as is usually stated.

B. From the Pathological Stand-point.

1. Osteitis deformans is a disease affecting the skull, vertebræ, and certain of the long bones. Its essential pathologic characteristics are:

a. Absorption of the compact substance causing enlargement and confluence of the Haversian canals.

b. Formation of new bone which runs diffusely through the affected

and the adjacent healthy portions. This new bone remains uncalcified, and is in turn reabsorbed.

c. The conversion of the medullary substance into a vascular connective tissue containing fat cells, giant cells, and leukocytes. In a small proportion of the reported cases cysts filled with gelatinous material and giant-celled sarcomata occur in the medulla.

d As a consequence of these three processes, the ordinary relations of the compact substance and medulla are destroyed. The bones become exceedingly thickened and asymmetrical, but since the new bone tissue remains uncalcified its elasticity permits of great deformity of the long bones from the weight of the body, and fractures do not occur.

2. The whole picture of osteitis deformans from its pathologic aspect is so very characteristic that it must be considered a distinct disease, and its pathologic diagnosis is correspondingly easy.

3. The etiology of the condition is as obscure as when Paget first described it. Some predisposing tendency, probably trophic, must be assumed, and the exciting cause may be mechanical—in the skull, extremes of heat and cold, and in the vertebræ and long bones the ordinary traumata to which these bones are exposed. Lesions of the nervous system are inconstant and rare, and are probably not a causal factor.

THE SPINAL FORM OF ARTHRITIS DEFORMANS.

Remarks Introductory to a Discussion on the Subject.

By WILLIAM OSLER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

Few diseases present more interesting problems for solution than arthritis deformans: Are there not several disorders embraced under this term? Is it a chronic infection? or is it primarily an affection of the nervous system? and, above all, the question of treatment? Let me briefly call your attention to one or two points. Of the full-blown disorder we can recognize at least three varieties—the remarkable form in children, associated with enlarged spleen and lymph glands; a variety with atrophy of the joint structures and ligamentous thickening, but without osteophytes, and a third, the more common picture, with nodosities, ring-bones, exostoses, etc. Nothing is more remarkable than the diversity in the clinical picture—the acute febrile onset and course of some cases, the painless course in one, the marked disturbances of sensation in another, the variations in the degree of wasting, and the tendency to early arrest in some, to progressive, disabling arthritis in others. Then, again, the localities involved. While in a majority of cases it is a polyarthritis, a single joint may be involved, or certain groups; the small joints of the hands and feet alone, or the large joints chiefly, or only the joints of the legs, or the joints of the spine.

It is to this spinal form that I wish to direct your attention. Perhaps the oldest known anatomic lesion, since it has been found in a mummy, an exceptional interest has been excited in the condition by the studies of von Bechterew, Marie, and others, who have attempted to separate at least two diseases, or, at any rate, well-marked varieties. Bechterew described an affection characterized by (1) rigidity of the spine, with fixation of the thorax; (2) kyphosis, chiefly of the upper dorsal spine, so that the head is bent forward; (3) weakness, with atrophy of the muscles of the trunk, neck, and extremities; (4) disturbances of sensation—paresthesiæ, pains, etc. The joints of the spine alone are involved. While at first he thought

the process a primary spondylitis deformans, later he adopted the view that the affection of the spine was secondary to a compression of the nerve roots by the thickening of the pia mater. This caused the pains, etc., and the weakness of the muscles of the trunk. The ankylosis resulted from the altered statics of the spinal column, which, losing the support of the muscles, flattened the cartilaginous disks and led to atrophy, and finally to union of the bones. Bechterew laid stress on heredity and injury as factors in the etiology.

The affection described by Marie (and also by Strümpell) as *spondylose rhizomelique*, or spondylitis with involvement of the roots of the limb, is characterized by the same rigidity of the spine, due to ankylosis, more or less extensive variable nervous features, and occasionally fixation of the thorax. The distinguishing feature is the involvement of other joints, usually of the shoulders and hips, or the hips alone, but in many cases the smaller joints as well. This Strümpell-Marie group, as it is called, is distinguished from the cases of the Bechterew type by the less pronounced nervous symptoms, and the more extensive involvement of the joints.

The following is a brief abstract of the cases which have been under my care recently:

CASE I.—Male, aged thirty-three years; seen January 18, 1899. There is no hereditary history; no injury or gonorrhea. There was rheumatic affection of the joints fourteen years ago, and for eleven years he has been much crippled; every joint in the body has been affected; there is much pain at times. He was able to work until three years ago. He has never had any pain in the back, but for eighteen months or more has had to stoop from the hips. He has had spells of fever at times. There are present pigmentation of the skin, enlargement of the spleen, rigidity of the entire spine, kyphosis at the junction of the dorsal and cervical vertebræ, moderate atrophy of the shoulder-girdle muscles; the thorax is almost immobile, the ankles and several smaller joints of the hands are thickened, the left shoulder is swollen, and there is crepitus on motion.

CASE II.—Male, aged fifty-two years; seen October 13, 1899. There is no hereditary history; no injury. Had "rheumatic" attacks in 1885, 1887, and 1891; the shoulders, hips, and wrists were involved. Since 1891 he has been gradually getting worse, and stiffness of the spine has gradually come on. The right shoulder is restricted in motion, and the left is tender. The right knee is enlarged. There is almost complete spinal rigidity and moderate kyphosis. There is complete thoracic immobility and no pain in the spine, but a little pain on turning. The dorsal muscles are singularly hard and firm.

CASE III.—Male, aged fifty-eight years; seen February 5, 1891. There is no hereditary history; no trauma. Had rheumatism four years ago; the right knee and ankle are swollen; has been in bed four months. His back began to get

sore and stiff, and he has been getting worse ever since. His head began to bend forward; for six months he could not bend his back. He has had much pain, also a great many boils; he has had pains, with numbness and tingling in legs. A tremor has gradually come on in the hands, and the voice has changed. Extreme grade of spinal rigidity, with kyphosis, and marked atrophy of muscles of the back, shoulder girdles, and of the hands; characteristic movements of paralysis agitans; crepitation in joints of arms; no swelling. Extensive arthritis of right hip-joint, with shortening of the leg; both knees are slightly swollen; no osteophytes.

CASE IV.—Male, aged thirty years; seen June 7, 1900. There is no hereditary history; no trauma. Five years ago he had rheumatic attack in one hip; had rheumatism again in February, 1899, and has had ever since progressive difficulty in movement of the spine, and pains in the back and sides. Spine immobile; slight kyphosis; chest flat, and movements much restricted. Pains are now about the shoulders, and in the back when he attempts movement; there is no impairment of sensation; there is moderate wasting of the muscles of the trunk; hips and shoulders are not affected; the right elbow is involved; he cannot fully extend the arm; knee-jerks are exaggerated.

CASE V.—Female, aged seventy-two years, was brought to my out-patient clinic in February, 1900. For several years has had gradual disability, owing to stiffening of the spine, with agonizing pains. Extreme kyphosis; difficulty in swallowing; no joints of the limbs are involved; there is wasting of the shoulder-girdle muscles, of the back, and of the arms; immobility of the thorax. She has pains of great severity in the back and sides, requiring two to four grains of morphin a day.

The position I wish to take in this discussion is that the forms described by von Bechterew, Strümpell, and Marie are not, as has been suggested, separate maladies, but are only varieties of arthritis deformans. It seems that my cases bear out this view very strongly.

Case I. had had extensive involvement of the peripheral joints, and when he came under observation they were very much thickened. He had complete rigidity of the spine, with atrophy of the shoulder-girdle muscles, and immobility of the thorax. He had had no pain. So also in Cases II., III., and IV. other joints were involved, while the spinal involvement was quite characteristic of the spondylitis deformans. Case V. alone had no other involvement of the joints. She had, too, in a more severe form the agonizing pains which have been described in some cases, and a great degree of wasting of the shoulder-girdle muscles. Some years ago in the Museum at Buffalo I was much interested in a remarkable skeleton illustrating the spondylitis deformans, and I suggested to Dr. Stockton that he should bring it here, as it illustrates the anatomic condition in a remarkable way. It is of special value, as it shows the involvement of other joints.

SKELETON OF THE SPINAL FORM OF ARTHRITIS DEFORMANS.

EXHIBITED BY D. S. LAMB, M.D.,
OF WASHINGTON, D. C.

BY request of Dr William Osler, Dr. Lamb, of the Army Medical Museum, showed the following specimens from the collection:

A specimen of a portion of the spine of the famous horse "Chester Morris," showing arthritis deformans.

The greater part of the spinal column of a human adult, showing arthritis deformans in cervical, thoracic, and lumbar regions. No history. The specimen came from the Gibson collection, Richmond, Va., which was bought by the Museum.

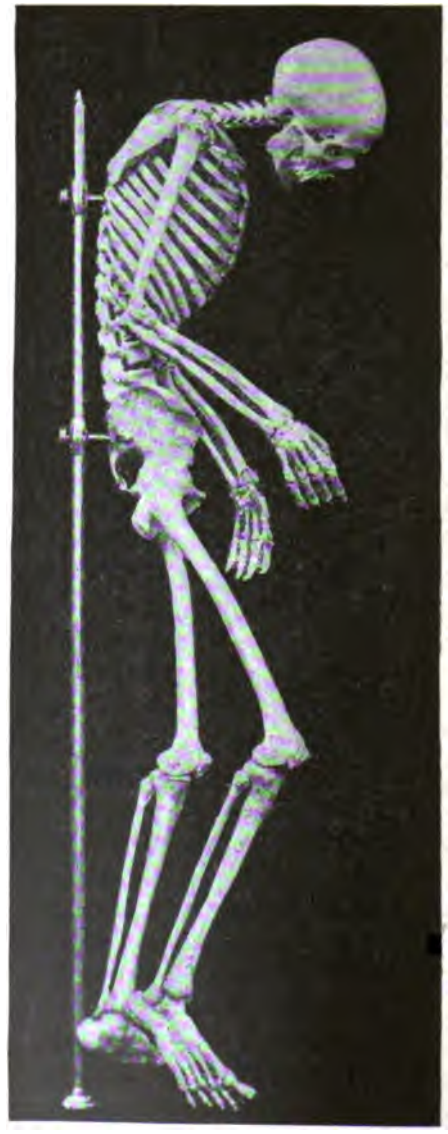
Skeleton showing arthritis deformans of the spine of a human adult, with marked posterior curvature. Obtained by Prof. William H. Dall, United States National Museum, Washington, D. C., from an Aleutian village community-house, of stone, belonging to the latter part of the Hunting period, near Ulakhta Head, Amaknak Island, Bay of Unalashka. Of course, no history.

SKELETON OF THE SPINAL FORM OF ARTHRITIS DEFORMANS.

EXHIBITED BY CHARLES G. STOCKTON, M.D.,
OF BUFFALO, N. Y.

THIS interesting, and in some respects unique, skeleton I present at the request of Dr. Osler. It comes from the Museum of the Medical Department of the University of Buffalo, to which it was presented by Dr. Roswell Park. I had the opportunity of seeing during life the man from whom the skeleton came, and of making some clinical observation upon him. Born in England of mixed French and English parentage, he was at the time of his death forty-four years old. He was received as a patient at the Erie County Almshouse in 1878, at which time he had lived eleven years in the United States. He died after having been in the hospital fifteen years. The man was of intemperate habits, and was by occupation a stonemason. He entered the institution because of disability, the result of arthritis, which began some five years before as the continuation of a gonorrheal arthritis. The joint affection was progressive after his entrance, and for about three years before his death he was unable to move any joint in his body. It was necessary to extract his incisor teeth so that he could be fed. He complained of much pain, which was relieved by taking ten grains of acetanilid in whiskey. He was much constipated. The complexion was very dark from pigmentation. He became toward the end very much emaciated, and there was marked muscular atrophy, most pronounced in the legs. The attitude assumed by the skeleton probably resulted from the posture taken by the patient as he was propped up in bed. All the vertebræ and the pelvis were united by strong ankylosis, the inferior maxillary bone being absolutely fixed. Some of the other joints, that were perfectly immovable during life, after preparation of the skeleton were found to admit of

slight motion. A singular feature is the deep groove that appears on either side of the pubis, extending downward and involving the head



General osteoarthritis, with multiple synostoses ("ossified man"). (PARK.)

of the femur. The grooves through which pass the tendons of muscles are found to be unusually deep.

DISCUSSION.

DR. SACHS: I was interested in this subject for a number of years, and about a year ago published a paper which I dare say is not familiar to the majority of the gentlemen here. To distinguish between the two types that Dr. Osler has referred to has given us much trouble, and I am glad to hear Dr. Osler say that he is in favor of considering them both as arthritis deformans. The argument that the one form is secondary to spinal-root disease is difficult to accept. The Marie type is one we can recognize very easily, but the name that has been proposed by the French authors—*spondylose rhizomelique*—is not particularly fitting, I think. That case which corresponded in every other respect to the Marie type should be accepted, I think, as a case of widespread arthritis deformans. A day or so before leaving New York I had the opportunity of seeing a case of the Bechterew type. It was in a patient thirty-five years of age, who was received into the hospital complaining of pain and inability to move the right arm. I found complete ankylosis of the upper dorsal portion of the spinal column. The pain radiated over the right thorax, and there was atrophy only of the muscles innervated from that special segment.

DR. J. P. CROZER GRIFFITH: I would like to show in this connection a specimen from a case reported some years ago by the late Dr. Charles Herwirsch, then one of my hospital assistants. It was published by him, but in a journal so little known that it is doubtful whether any of those present have seen the photograph which accompanied the report. This, too, I will pass around with the specimen.

The case was that of a woman, aged seventy-one years, who had been perfectly healthy until about the age of sixty-four years, when she began to develop an enlargement of the head, and gradually grew more and more stupid and apathetic until she barely recognized or noticed her friends. I saw her only very casually before death, and although noticing the size of her head, which suggested hydrocephalus, I made no examination of her. She came to autopsy, and still the head was supposed to be hydrocephalic. But when the operator began to saw off the calvarium, all of us standing about wondered why he took such a very long time to get through the bone. We were even disposed to criticise silently his lack of skill. The calvarium, which I exhibit, explains, however, the reason for the delay. You see how enormously thickened the bone is, and how hard it is in some places, although rarefied in others. As you see it it illustrates a typical case of hyperostosis cranii.

Yet while the autopsy was going on I took occasion to feel some of the other bones of the body, and discovered that the pelvis and the bones of the upper and lower extremities were also very greatly thickened. This fact at once takes the case out of the class of hyperostosis cranii, or leontiasis ossea, if we limit the term as some have done, and put it in that of osteitis deformans. Yet here, too, it does not fit altogether, since in this latter condition, according to some statements, the head should not be greatly enlarged. It seems to me very likely that these two diseases shade into each other very decidedly, and that a sharp separation is impossible in the present state of our knowledge.

I wish also to show photographs of a condition seen in a boy of about eight years, whose case I hope to report in full another time. This child had a head very typically that of hyperostosis cranii, yet the bones of the extremities were greatly thickened also, as in this woman. Now, inasmuch as osteitis deformans is a disease of older years, this case should not be placed in that category; yet to all appearances the gross lesions, at least, are similar to cases of the adult disease—another reason for believing that it is impossible to separate sharply from each other some of these diseases of the bone.

DR. CABOT: I wish to speak of two points in regard to Dr. Osler's paper. First, the distinction between the acute destructive and the chronic productive forms. The study of Dr. Goldthwait's specimens, obtained largely through operations on these cases, has convinced me that these two processes, instead of being two different stages or phases of one disease, are practically different diseases. The second point I want to mention concerns the relief given to the spinal cases by mechanical support. The relief thus secured, say by the use of a plaster jacket, is sometimes very marked.

DR. PUTNAM: I would like to ask Dr. Packard if he thinks such cases as he described, and of which I have seen a number, where the head alone is enlarged, and especially in the anterior portion, should be differentiated from the cases of Paget's disease?

DR. PACKARD: In answer to Dr. Putnam, I would say that we know so little about these cases as yet that we are not ready even to classify them.

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